cortical spreading depression and **migraine**

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(Updated 6/14/04)

Nouchine Hadjikhani, Margarita Sanchez del Rio, Ona Wu, Denis Schwartz, Dick Bakker, Bruce Fischl, Kenneth K. Kwong, F. Michael Cutrer, Bruce R. Rosen, Roger B. H. Tootell, A. Gregory Sorensen, and Michael A. Moskowitz

Mechanisms of migraine aura revealed by functional MRI in human visual cortex

PNAS 98: 4687-4692; published online before print as 10.1073/pnas.071582498

"**Cortical spreading** depression (CSD) has been suggested to underlie **migraine** visual aura. However, it has been challenging to test this hypothesis in human cerebral cortex. Using high-field functional MRI with near-continuous recording during visual aura in three subjects, we observed blood oxygenation level-dependent (BOLD) signal changes that demonstrated at least eight characteristics of CSD, time-

George G. Somjen

Mechanisms of Spreading Depression and Hypoxic Spreading Depression-Like Depolarization

Physiol. Rev. 81: 1065-1096, 2001.

Spreading depression (SD) and the related hypoxic SD-like depolarization (HSD) are characterized by rapid and nearly complete depolarization of a sizable population of brain cells with massive redistribution of ions between intracellular and extracellular compartments, that evolves as a regenerative, "all-or-none" type process, and propagates slowly as a wave in brain tissue. This article reviews the characteristics of SD and HSD and the main hypotheses that have been proposed to explain them. Both SD and HSD are composites of concurrent processes. Antagonists of N-methyl-D-aspartate (NMDA) channels or voltage-gated Na(+) or certain types of Ca(2+) channels can

locked-to percept/onset of the aura. Initially, a focal increase in BOLD signal (possibly reflecting vasodilation), developed within extrastriate cortex (area V3A). This BOLD change progressed contiguously and slowly (3.5 +/- 1.1 mm/min) over occipital cortex, congruent with the retinotopy of the visual percept. Following the same retinotopic progression, the BOLD signal then diminished (possibly reflecting vasoconstriction after the initial vasodilation), as did the BOLD response to visual activation. During periods with no visual stimulation, but while the subject was experiencing scintillations, BOLD signal followed the retinotopic progression of the visual percept. These data strongly suggest that an electrophysiological event such as CSD generates the aura in human visual cortex." [Full Text]

Cao Y, Welch KM, Aurora S, Vikingstad EM.

Functional MRI-BOLD of visually triggered headache in patients with migraine.

Arch Neurol. 1999 May;56(5):548-54.

"BACKGROUND: **Spreading** depression of Leao has been hypothesized as the basis for the visual aura of the **migraine** attack, supported by cerebral blood flow measurements of **spreading** hypoperfusion. The early depolarizing or activation phase of experimental **spreading** depression, however, is associated with a transient but pronounced cerebral blood flow increase that precedes **spreading** hypoperfusion. OBJECTIVE: To study this early phase of the **migraine** attack, we investigated visually triggered attacks of headache and visual symptoms using a red-green checkerboard stimulus in patients with **migraine**. INTERVENTIONS: We studied occipital cortex activation during visual stimulation by measuring occipital cortex perfusion with functional magnetic resonance imaging-blood oxygenation level-dependent contrast in 10 patients with **migraine** with aura and 2 patients with **migraine** without aura and 6 healthy subjects. RESULTS: In 6 patients with **migraine** with aura and 2 patients with **migraine** without aura, their typical headache with (n = 2) or without visual change was visually triggered at 7.3 minutes (mean time) after visual stimulation began. In 5 of these patients, the onset of headache or visual change, or both, was preceded by suppression of initial activation (mean onset time, 4.3 minutes; P<.001) The suppression slowly propagated into contiguous occipital cortex at a rate ranging from 3 to 6 mm/ min. This neuronal suppression was accompanied by baseline contrast intensity increases that indicated vasodilatation and tissue hyperoxygenation. CONCLUSIONS: We conclude that visually triggered headache and visual change in patients with **migraine** is accompanied by **spreading** suppression of initial neuronal activation and increased occipital cortex oxygenation. We postulate that this **spreading** suppression may be associated with initial activation of a **migraine** attack, independent of whether there are associated aura symptoms. We further postulate that there may be an association between vasodilation accompanying the initial stage of suppression and the induction of headache." [Abstract]

Bolay H, Reuter U, Dunn AK, Huang Z, Boas DA, Moskowitz MA.

Intrinsic brain activity triggers trigeminal meningeal afferents in a migraine model.

Nat Med. 2002 Feb;8(2):136-42.

"Although the trigeminal nerve innervates the meninges and participates in the genesis of **migraine** headaches, triggering postpone or mitigate SD or HSD, but it takes a combination of drugs blocking all known major inward currents to effectively prevent HSD. Recent computer simulation confirmed that SD can be produced by positive feedback achieved by increase of extracellular K(+) concentration that activates persistent inward currents which then activate K(+) channels and release more K(+). Any slowly inactivating voltage and/or K(+)-dependent inward current could generate SD-like depolarization, but ordinarily, it is brought about by the cooperative action of the persistent Na(+) current I(Na,P) plus NMDA receptor-controlled current. SD is ignited when the sum of persistent inward currents exceeds persistent outward currents so that total membrane current turns inward. The degree of depolarization is not determined by the number of channels available, but by the feedback that governs the SD process. Short bouts of SD and HSD are well tolerated, but prolonged depolarization results in lasting loss of neuron function. Irreversible damage can, however, be avoided if Ca(2+) influx into neurons is prevented. [Full Text]

Read SJ, Smith MI, Hunter AJ, Parsons AA.

Enhanced nitric oxide release during cortical spreading depression following infusion of glyceryl trinitrate in the anaesthetized cat.

Cephalalgia. 1997 May;17(3):159-65.

"Intravenous infusion of glyceryl trinitrate (GTN) into migraineurs induces an immediate headache followed by **migraine**. We studied the effect of GTN (0.25 microgram kg-1 min-1) on local cerebrovascular laser Doppler flux (rCBFLDF), artery diameter and NO concentration (selective NO microelectrode) in the pial middle cerebral artery perfusion territory of the anaesthetized cat, at rest and during **cortical spreading** depression (SD). GTN infusion induced a significant increase in pial artery diameter, rCBFLDF, and NO concentration. Following termination of infusion, NO concentrations remained significantly elevated above controls for 60 min, other parameters returned to baseline within 10 min (p < 0.05, ANOVA, post hoc Dunnett's multiple comparison procedure). Two hours after termination of infusion KCl-evoked SD was initiated. GTN-treated animals exhibited significantly (p < 0.05, Kruskal-Wallis) elevated SD-induced NO release compared to controls. All other parameters remained unaffected. Our results demonstrate that GTN induces a prolonged increase in local NO concentrations and enhances SD-induced NO release." [Abstract]

Christiansen I, Thomsen LL, Daugaard D, Ulrich V, Olesen J.

Glyceryl trinitrate induces attacks of migraine without aura in sufferers of migraine with aura.

Cephalalgia. 1999 Sep;19(7):660-7; discussion 626.

"**Migraine** with aura and **migraine** without aura have the same pain phase, thus indicating that **migraine** with aura and **migraine** without aura share a common pathway of nociception. In recent years, increasing evidence has suggested that the messenger molecule nitric oxide (NO) is involved in pain mechanisms of **migraine** without aura. In order to clarify whether the same is true for **migraine** with aura, in the present study we examined the headache response to intravenous infusion of glyceryl trinitrate (GTN) (0.5 microg/kg/min for 20 min) in 12 sufferers of **migraine** with aura. The specific aim was to elucidate whether an aura and/or an attack of **migraine** without aura could be induced. Fourteen healthy subjects served as controls. Aura symptoms were not elicited in any subject. Headache was more severe in migraineurs than in the controls during and immediately after

mechanisms remain controversial and poorly understood. Here we establish a link between **migraine** aura and headache by demonstrating that **cortical spreading** depression, implicated in **migraine** visual aura, activates trigeminovascular afferents and evokes a series of **cortical** meningeal and brainstem events consistent with the development of headache. **Cortical spreading** depression caused long-lasting blood-flow enhancement selectively within the middle meningeal artery dependent upon trigeminal and parasympathetic activation, and plasma protein leakage within the dura mater in part by a neurokinin-1-receptor mechanism. Our findings provide a neural mechanism by which extracerebral cephalic blood flow couples to brain events; this mechanism explains vasodilation during headache and links intense neurometabolic brain activity with the transmission of headache pain by the trigeminal nerve." [Abstract]

Sanchez-Del-Rio M, Reuter U.

Migraine aura: new information on underlying mechanisms.

Curr Opin Neurol. 2004 Jun;17(3):289-293.

"PURPOSE OF REVIEW: Since the initial description of **cortical spreading** depression by Leao, evidence that **cortical spreading** depression is the underlying pathomechanism of **migraine** aura has increased. The purpose of this review is to describe the ultimate genetic and molecular mechanisms of **migraine** aura. RECENT FINDINGS: It has been debated how a primarily **cortical** phenomenon (aura phase) may activate trigeminal fibres (headache phase). Recent data have demonstrated a link between **cortical** events and activation of the pain-sensitive structures of the dura mater. The initial **cortical** hyperperfusion in **cortical spreading** depression is partly mediated by the release of trigeminal and parasympathetic neurotransmitters from perivascular nerve fibres, whereas delayed meningeal blood flow increase is mediated by a trigeminal-parasympathetic brainstem connection. With regard to molecular mechanisms, **cortical spreading** depression upregulates a variety of genes coding for COX-2, TNF-alpha and IL-1beta, galanin or metalloproteinases. The activation of metalloproteinases leads to leakage of the blood-brain barrier, allowing potassium, nitric oxide, adenosine and other products released by **cortical spreading** depression to reach and sensitize the dural perivascular trigeminal afferents. In familial hemiplegic **migraine**, new mutations have been described in chromosome 1q23, leading to a haploinsufficiency of the sodium/potassium pump, producing an increase in intracellular calcium, similar to the CACNA1A mutation. SUMMARY: Recent studies have helped unravel the basic mechanisms involved in **migraine** aura. Far from being a simple phenomenon, a sequence of events leads from the cortex to the activation of pain-sensitive structures. The role of the brainstem is still poorly described. The identification of target molecules may provide new therapies." [Abstract]

Gursoy-Ozdemir, Yasemin, Qiu, Jianhua, Matsuoka, Norihiro, Bolay, Hayrunnisa, Bermpohl, Daniela, Jin, Hongwei, Wang, Xiaoying, Rosenberg, Gary A., Lo, Eng H., Moskowitz, Michael A.

Cortical spreading depression activates and upregulates MMP-9

J. Clin. Invest. 2004 113: 1447-1455

"**Cortical spreading** depression (CSD) is a propagating wave of neuronal and glial depolarization and has been implicated

GTN infusion (p=0.037) as well as during the following 11 h (p = 0.008). In the controls, the GTN-induced headache gradually disappeared, whereas in migraineurs peak headache intensity occurred at a mean time of 240 min post-infusion. At this time the induced headache in 6 of 12 migraineurs fulfilled the diagnostic criteria for **migraine** without aura of the International Headache Society. The results therefore suggest that NO is involved in the pain mechanisms of **migraine** with aura. Since **cortical spreading** depression has been shown to liberate NO in animals, this finding may help our understanding of the coupling between **cortical spreading** depression and headache in **migraine** with aura." [Abstract]

Wahl M, Schilling L, Parsons AA, Kaumann A.

Involvement of calcitonin gene-related peptide (CGRP) and nitric oxide (NO) in the pial artery dilatation elicited by cortical spreading depression.

Brain Res. 1994 Feb 21;637(1-2):204-10.

"The aim of the present study was to examine whether the initial transient arterial dilatation during **cortical spreading** depression (CSD) was mediated by the release of calcitonin gene-related peptide (CGRP) and/or nitric oxide (NO). This question is of interest as the initial phase of CSD appears to be a model of events occurring during functional hyperemia and during the first period of classic **migraine**. Using an open cranial window technique, pial arterial diameter in the parietal cortex of cats was recorded with an image splitting method. Employing micropuncture technique, perivascularly applied CGRP8-37 did not alter the resting diameter of pial arteries but antagonized concentration dependently (5 x 10(-9)-10(-6) M) the dilatation (35%) due to 5 x 10(-8) M CGRP. NG-Nitro-L-Arginine (NOLAG, 10(-4) M) also had no effect on resting diameter of pial arteries, indicating that their resting tone is neither mediated by a continuous release of CGRP nor of NO. CSD was triggered by a remote intracortical injection of KCl (150 mM) and recorded by a microelectrode placed adjacent to the artery under investigation. CSD elicited a transient negative DC shift which was accompanied by a peak dilatation of 44 +/- 5.2% (S.E.M.). This dilatation was reduced by approximately 50% during topical application of 10(-7) M CGRP8-37 and 10(-4) M NOLAG each. A 75% inhibition of the CSD-induced dilatation was found during simultaneous application of both compounds. These data indicate that the initial dilatation during CSD is mediated, at least in part, by a release of CGRP and NO." [Abstract]

Piper RD, Edvinsson L, Ekman R, Lambert GA.

Cortical spreading depression does not result in the release of calcitonin gene-related peptide into the external jugular vein of the cat: relevance to human migraine.

Cephalalgia. 1993 Jun;13(3):180-3; discussion 149.

"There is circumstantial evidence that **cortical spreading** depression (SD) may account for the scotoma and the "**spreading cortical** oligemia" seen during **migraine** with aura. It has been shown that calcitonin gene-related peptide (CGRP) is increased in blood taken from the external jugular vein (EJV) in humans during **migraine** and after stimulation of the trigeminal ganglion. To test the hypothesis that **cortical** SD may elevate the concentration of this vasoactive peptide in the EJV during **migraine**, we have measured its concentration in the external jugular vein of cats during **cortical** SD. This study demonstrates that SD has no effect on the concentration of CGRP either during the passage of a wave of **spreading** depression across the cortex

in disorders of neurovascular regulation such as stroke, head trauma, and **migraine**. In this study, we found that CSD alters blood-brain barrier (BBB) permeability by activating brain MMPs. Beginning at 3-6 hours, MMP-9 levels increased within cortex ipsilateral to the CSD, reaching a maximum at 24 hours and persisting for at least 48 hours. Gelatinolytic activity was detected earliest within the matrix of **cortical** blood vessels and later within neurons and pia arachnoid (> or =3 hours), particularly within piriform cortex; this activity was suppressed by injection of the metalloprotease inhibitor GM6001 or in vitro by the addition of a zinc chelator (1,10-phenanthroline). At 3-24 hours, immunoreactive laminin, endothelial barrier antigen, and zona occludens-1 diminished in the ipsilateral cortex, suggesting that CSD altered proteins critical to the integrity of the BBB. At 3 hours after CSD, plasma protein leakage and brain edema developed contemporaneously. Albumin leakage was suppressed by the administration of GM6001. Protein leakage was not detected in MMP-9-null mice, implicating the MMP-9 isoform in barrier disruption. We conclude that intense neuronal and glial depolarization initiates a cascade that disrupts the BBB via an MMP-9-dependent mechanism." [Full Text]

van den Maagdenberg AM, Pietrobon D, Pizzorusso T, Kaja S, Broos LA, Cesetti T, van de Ven RC, Tottene A, van der Kaa J, Plomp JJ, Frants RR, Ferrari MD.

A Cacna1a knockin migraine mouse model with increased susceptibility to cortical spreading depression.

Neuron. 2004 Mar 4;41(5):701-10.

"**Migraine** is a common, disabling, multifactorial, episodic neurovascular disorder of unknown etiology. Familial hemiplegic **migraine** type 1 (FHM-1) is a Mendelian subtype of **migraine** with aura that is caused by missense mutations in the CACNA1A gene that encodes the alpha(1) subunit of neuronal Ca(v)2.1 Ca(2+) channels. We generated a knockin mouse model carrying the human pure FHM-1 R192Q mutation and found multiple gain-of-function effects. These include increased Ca(v)2.1 current density in cerebellar neurons, enhanced neurotransmission at the neuromuscular junction, and, in the intact animal, a reduced threshold and increased velocity of **cortical spreading** depression (CSD; the likely mechanism for the **migraine** aura). Our data show that the increased susceptibility for CSD and aura in **migraine** may be due to **cortical** hyperexcitability. The R192Q FHM-1 mouse is a promising animal model to study **migraine** mechanisms and treatments." [Abstract]

Diener HC.

Positron emission tomography studies in headache.

Headache. 1997 Nov-Dec;37(10):622-5.

"Positron emission tomography (PET) allows the quantitative measurement of regional cerebral flow (rCBF) in humans in quantitative terms. Gross changes in rCBF are due to variation in vessel diameter. Changes of rCBF also reflect synaptic activity (inhibition and excitation). Therefore, PET was used to monitor changes in blood flow during the aura and headache phase of a **migraine** attack and to investigate focal areas of increased or decreased blood flow, e.g., in the brain stem and midbrain. Hemispheric rCBF was unchanged in spontaneous **migraine** attacks without aura. This was true for the headache side as well as for the nonheadache side. Sumatriptan had no effects on cerebral blood flow. Regional or, 60 min later, during the period of post-SD **cortical** oligemia." [Abstract]

Wang M, Obrenovitch TP, Urenjak J.

Effects of the nitric oxide donor, DEA/NO on cortical spreading depression.

Neuropharmacology. 2003 Jun;44(7):949-57.

"**Cortical spreading** depression (CSD) is a transient disruption of local ionic homeostasis that may promote **migraine** attacks and the progression of stroke lesions. We reported previously that the local inhibition of nitric oxide (NO) synthesis with Nomega-nitro-L-arginine methyl ester (L-NAME) delayed markedly the initiation of the recovery of ionic homeostasis from CSD. Here we describe a novel method for selective, controlled generation of exogenous NO in a functioning brain region. It is based on microdialysis perfusion of the NO donor, 2-(N,N-diethylamino)-diazenolate-2-oxide (DEA/NO). As DEA/NO does not generate NO at alkaline pH, and as the brain has a strong acid-base buffering capacity, DEA/NO was perfused in a medium adjusted at alkaline (but unbuffered) pH. Without DEA/NO, such a microdialysis perfusion medium did not alter CSD. DEA/NO (1, 10 and 100 microM) had little effect on CSD by itself, but it reversed in a concentration-dependent manner the effects of NOS inhibition by 1 mM L-NAME. These data demonstrate that increased formation of endogenous NO associated with CSD is critical for subsequent, rapid recovery of cellular ionic homeostasis. In this case, the molecular targets for NO may be located either on brain cells to suppress mechanisms directly involved in CSD genesis, or on local blood vessels to couple flow to the increased energy demand associated with CSD." [Abstract]

Fabricius M, Akgoren N, Lauritzen M.

Arginine-nitric oxide pathway and cerebrovascular regulation in cortical spreading depression.

Am J Physiol. 1995 Jul;269(1 Pt 2):H23-9.

"Nerve cells release nitric oxide (NO) in response to activation of glutamate receptors of the N-methyl-D-aspartate (NMDA) subtype. We explored the hypothesis that NO influences the changes of cerebral blood flow (CBF) during **cortical spreading** depression (CSD), which is known to be associated with NMDA receptor activation. CBF was monitored in parietal cortex by laser-Doppler flowmetry in halothane-anesthetized rats. Under control conditions, CSD induced regular changes of CBF, which consisted of four phases: a brief hypoperfusion before the direct current (DC) shift; a marked CBF rise during the DC shift; followed by a smaller, but protracted increase of CBF; and a prolonged CBF reduction (the oligemia). NO synthase inhibition by intravenous and/or topical application of NG-nitro-L-arginine enhanced the brief initial hypoperfusion, but the CBF increases and the oligemia were unchanged. L-Arginine prevented the development of the prolonged oligemia after CSD but had no influence on the marked rise of CBF during CSD. Animals treated with L-arginine recovered the reduced vascular reactivity to hypercapnia after CSD much faster than control rats. Functional denervation of **cortical** and pial arterioles by tetrodotoxin accentuated the pre-CSD hypoperfusion and the oligemia but did not affect the CBF increases. The results suggest that NO is important for the changes of cerebrovascular regulation following CSD. The observations may have clinical importance, since CBF changes during **migraine** may be triggered by CSD." [Abstract]

Wolf T, Lindauer U, Obrig H, Dreier J, Back T, Villringer A, Dirnagl U.

cerebral blood flow was increased in midline brain stem structures during the headache phase, but also when the headache had been treated with sumatriptan. This persisting increased activity might reflect activity of a presumed **migraine** center in the brain stem. These changes are specific for **migraine** attacks and are not seen during attacks of cluster headache. Positron emission tomography measurements in the early phase of a **migraine** attack in a single subject showed flow reductions in the occipital cortex **spreading** forwards; an observation which would be compatible with the existence of **spreading** depression in humans. Our attempts to study the aura phase with PET have, to date, been unsuccessful." [Abstract]

Lauritzen M, Skyhoj Olsen T, Lassen NA, Paulson OB.

Changes in regional cerebral blood flow during the course of classic migraine attacks.

Ann Neurol. 1983 Jun;13(6):633-41.

"Regional cerebral blood flow (rCBF) following carotid arteriography was studied in thirteen patients with classic **migraine**. Using the 133xenon intraarterial injection method, rCBF was measured in 254 areas in one hemisphere. Nine patients developed a characteristic attack following arteriography and were examined by a series of rCBF studies, spaced by intervals of 5 to 10 minutes. A wave of reduced blood flow originating in the posterior part of the brain and progressing anteriorly was observed in eight of the nine patients. The oligemia advanced at a speed of 2 mm per minute over the hemisphere, progressing anteriorly but not crossing the rolandic or sylvian sulcus. Typically, the **spreading** oligemia reached the primary sensorimotor area after symptoms from that area had begun and persisted there long after the focal symptoms had disappeared. The observed time course suggests that the focal symptoms are not secondary to the oligemia. We suggest that focal symptoms and blood flow changes may be secondary to **spreading** depression of Leao." [Abstract]

Russell MB, Olesen J.

A nosographic analysis of the migraine aura in a general population.

Brain. 1996 Apr;119 (Pt 2):355-61.

"The study presented here is the first detailed nosographic analysis of **migraine** aura, diagnosed using the criteria of the International Headache Society, in a sufficiently large sample for statistical analysis. Of 4,000 people, 163 had **migraine** with aura. Sixty-two had attacks of **migraine** aura with headache as well as **migraine** aura without headache, and seven had exclusively **migraine** aura without headache. Visual symptoms were most frequent (99%), followed by sensory (31%), aphasic (18%) and motor (6%) symptoms. Those with several types of aura symptoms had visual aura in virtually every attack, while sensory, motor and aphasic aura were present only in a small number of their attacks. The typical visual aura starts as a flickering, uncoloured, zig-zag line in the centre of the visual field and affect the central vision. It gradually progresses towards the periphery of one hemifield and often leaves a scotoma. The typical sensory aura is unilateral, starts in the hand, progresses towards the arm and then affects the face and tongue. The typical motor aura is half-sided and affects the hand and arm. The visual, sensory and aphasic auras rarely lasted > 1 h, while the motor aura did in 67% (six out of nine). Four people had exclusively acute onset visual aura. The duration of the aura and the

Systemic nitric oxide synthase inhibition does not affect brain oxygenation during cortical spreading depression in rats: a noninvasive near-infrared spectroscopy and laser-Doppler flowmetry study.

J Cereb Blood Flow Metab. 1996 Nov;16(6):1100-7.

"**Cortical spreading** depression (CSD) has been implicated in the **migraine** aura and in stroke. This study demonstrates near-infrared spectroscopy (NIRS) for the first time as capable of noninvasive on-line detection of CSD in the pentobarbital-anesthetized rat. CSD was accompanied by a brief and rapid increase of regional CBF (by laser-Doppler flowmetry) to 200-400% baseline. NIRS demonstrates that this hyperperfusion is associated with concentration increases of oxyhemoglobin, while deoxyhemoglobin decreases. Simultaneously, oxygen partial pressure, measured on the brain surface with a solid-state polarographic probe, was shown to be raised by at least 14 mm Hg during CSD. Oxygen-dependent phosphorescence life-time quenching measurements confirmed this finding. NIRS data on cytochrome aa3, however, showed a CSD-related shift toward a more reduced state, despite raised blood oxygenation. This may suggest either limited O2 transport from the blood to mitochondria or decreased oxygen utilization during CSD as supposed by theories about compartmentalization of energy metabolism favoring glycolytic rather than aerobic energy supply during CSD. However, the data on cytochrome aa3 warrant caution and are discussed critically. Nitric oxide synthase inhibition by systemic application of N'-nitro-L-arginine had no significant effect on the perfusion response or the tissue PO2 during CSD. During most CSD episodes, a brief decrease in MABP by 4-8 mm Hg was noted that might be caused by functional decortication during CSD." [Abstract]

Richter F, Ebersberger A, Schaible HG.

Blockade of voltage-gated calcium channels in rat inhibits repetitive cortical spreading depression.

Neurosci Lett. 2002 Dec 13;334(2):123-6.

"Blockers of L-, N-, and P/Q-type voltage-gated calcium channels (VGCCs) were topically applied to the **cortical** surface of anaesthetized adult rats to study their role in **cortical spreading** depression (CSD), a correlate of the **migraine** aura. By pricking the brain, single CSD could still be elicited after blockade of the three different types of VGCCs as in the untreated brain. Topical KCl application to the untreated cortex resulted in repetitive CSD. However, after application of blockers at either L-, or N-, or P/Q-type VGCCs to the **cortical** surface, application of KCl elicited only one or very few CSD, and their repetition rate was dramatically reduced. The results suggest that **cortical** excitability resulting in repetitive CSD is markedly influenced by N- and P/Q-type VGCCs and less by L-type VGCCs." [Abstract]

Shimazawa M, Hara H, Watano T, Sukamoto T.

Effects of Ca2+ channel blockers on cortical hypoperfusion and expression of c-Fos-like immunoreactivity after cortical spreading depression in rats.

Br J Pharmacol. 1995 Aug;115(8):1359-68.

"1. We examined the effects of two Ca2+ channel blockers, lomerizine (KB-2796) and flunarizine, on the **cortical** hypoperfusion (measured by hydrogen clearance and laser Doppler flowmetry methods) and **cortical** c-Fos-like immunoreactivity that follow KCl-induced **cortical spreading** depression in anaesthetized rats. **Cortical spreading** depression

characteristics of the ensuing headache were typical for **migraine** with aura, suggesting that acute onset aura is a real phenomenon. Headache followed the aura in 93%, headache and aura occurred simultaneously in 4% and aura followed headache in 3%. The characteristic spread of each symptom and the sequence of different symptoms suggest that **cortical spreading** depression is the mechanism underlying the **migraine** aura. Our results do not suggest that alterations of the diagnostic criteria of the International Headache Society are needed. The intra-individual variation of aura symptoms shown in this study indicates that a simplification of the International Classification of Diseases, Neurological Adaptation is appropriate." [Abstract]

Shibata K, Osawa M, Iwata M.

Pattern reversal visual evoked potentials in classic and common migraine.

J Neurol Sci. 1997 Feb 12;145(2):177-81.

"Pattern reversal visual evoked potentials (PVEPs) to transient checkerboard were recorded in 19 patients with **migraine** with visual aura (i.e., classic **migraine**), 14 patients with **migraine** without aura (i.e., common **migraine**) in the interictal period and 43 normal subjects. Latencies and amplitudes of PVEPs in each group were analyzed. In classic **migraine** patients, P100 amplitude was significantly higher than in normal subjects ($p < 0.01$), whereas latencies of PVEPs did not significantly differ. There were no significant differences between the common **migraine** and normal subjects, nor within the classic and common **migraine** groups in latencies and amplitudes of PVEP. Four patients with classic **migraine** underwent PVEPs during or 1-2 h immediately after their **migraine** attacks. Two of these patients who underwent PVEPs 1.5-2 h after their attacks showed abnormally increased PVEP amplitudes. These results suggest that there are different pathophysiologies in the visual pathway between classic and common **migraine** and furthermore, classic **migraine** patients in interictal periods may have hyperexcitability in the visual pathway and that the increased amplitude of PVEPs after attacks may be due to **cortical spreading** depression." [Abstract]

Shibata K, Osawa M, Iwata M.

Pattern reversal visual evoked potentials in migraine with aura and migraine aura without headache.

Cephalalgia. 1998 Jul-Aug;18(6):319-23.

"Pattern reversal visual evoked potentials (PVEPs) were recorded in 20 patients with **migraine** with aura (MA), 19 patients with **migraine** without headache (**migraine** equivalent; ME) during interictal periods, and 34 normal subjects. All **migraine** patients had hemianopsia or fortification spectra during attacks. In both MA and ME patients of less than 49 years of age, there were significant ($p<0.01$) differences in amplitude of PVEPs at the mid-occipital and contralateral to visual aura electrode sites compared to normal subjects. Amplitude of PVEPs in MA and ME showed significant ($p<0.001$) increases when recorded soon after attacks, especially within 10 days. There was a significant ($p<0.01$) correlation between percentage asymmetries and the duration of illness in both MA and ME. We conclude from our PVEP findings that **cortical spreading** depression remains the most likely explanation for the **migraine** visual aura." [Abstract]

de Tommaso M, Sciruicchio V, Guido M, Sasanelli G,

was induced by application of 1 M KCl for 30 s to the **cortical** surface, 3.0 mm posterior to the area of cerebral blood flow measurement. 2. In control rats, KB-2796 (0.3 and 1 mg kg-1, i.v.) dose-dependently increased cerebral blood flow significantly at 30 min and 15 min, respectively, after its administration. Flunarizine (1 mg kg-1, i.v.) significantly increased cerebral blood flow 15 min after its administration. In contrast, dimetotiazine (3 mg kg-1, i.v.), a 5-HT2 and histamine H1 antagonist, failed to affect cerebral blood flow significantly. 3. After KCl application to the cortex, cerebral blood flow monitored by the laser Doppler flowmetry method increased transiently, for a few minutes, then fell and remained approximately 20 to 30% below control for at least 60 min. Cerebral blood flow monitored by the hydrogen clearance method was also approximately 20 to 30% below baseline for at least 60 min after KCl application. KB-2796 (0.3 and 1 mg kg-1, i.v.) and flunarizine (1 and 3 mg kg-1, i.v.) administered 5 min before KCl application inhibited the **cortical** hypoperfusion that followed KCl application, but dimetotiazine (1 and 3 mg kg-1, i.v.) did not. 4. An indicator of neuronal activation, c-Fos-like immunoreactivity, was detected in the ipsilateral, but not in the contralateral frontoparietal cortex 2 h after KCl application. No c-Fos-like immunoreactivity was seen on either side of the brain in the hippocampus, thalamus, striatum or cerebellum. 5. KB-2796 (1 mg kg-1, i.v.) and flunarizine (3 mg kg-1, i.v.), but not dimetotiazine (3 mg kg-1, i.v.), significantly attenuated the expression of c-Fos-like immunoreactivity in the ipsilateral frontoparietal cortex. 6. These findings suggest that the inhibitory effects of KB-2796 and flunarizine on the **cortical** hypoperfusion and expression of c-Fos-like immunoreactivity induced by **spreading** depression are mediated via the effects of $Ca(2+)$-entry blockade, which may include an increase in cerebral blood flow and the prevention of excessive Ca^{2+} influx into brain cells." [Abstract]

Tepper SJ, Rapoport A, Sheftell F.

The pathophysiology of migraine.

Neurolog. 2001 Sep;7(5):279-86.

"BACKGROUND: **Migraine** results from episodic changes in central nervous system physiologic function in hyperexcitable brain manifested by abnormal energy metabolism, lowered threshold for phosphene generation, and increased contingent negative variation. Human functional magnetic resonance imaging and magnetoencephology data strongly suggest that aura is caused by **cortical spreading** depression. REVIEW SUMMARY: Brain hyperexcitability may be caused by low magnesium levels, mitochondrial abnormalities with abnormal phosphorylation of adenosine 5'-diphosphate, a dysfunction related to nitric oxide, or calcium channelopathy. Low magnesium can result in opening of calcium channels, increased intracellular calcium, glutamate release, and increased extracellular potassium, which may in turn trigger **cortical spreading** depression. Mitochondrial dysfunction has been suggested by a low phosphocreatine:Pi ratio and a possible response by **migraine** patients to riboflavin prophylaxis. Nitroglycerine administration results in a delayed **migraine**-like headache in **migraine** patients but not in control patients, and a nonspecific nitric oxide synthase inhibitor aborted **migraine** at 2 hours in the majority of tested **migraine** patients compared to controls. Many patients with familial hemiplegic **migraine** have a missense mutation in the P/Q calcium channel, so that this form of **migraine**, at least, is associated with a demonstrable calcium channelopathy. CONCLUSIONS: The generation of **migraine** occurs centrally in the brain stem, sometimes preceded by **cortical spreading** depression and aura. Activation of the

Specchio LM, Puca FM.

EEG spectral analysis in migraine without aura attacks.

Cephalalgia. 1998 Jul-Aug;18(6):324-8.

"In 16 patients suffering from **migraine** without aura, we examined quantitative EEG and steady-state visual evoked potentials (SSVEPs) at 27 Hz stimulation during the critical phase of **migraine** and in attack-free periods. The main spontaneous EEG abnormalities found during the critical phase were the slowing and asymmetry of the dominant frequency in the alpha range. The amplitude of the SSVEP F1 component was significantly reduced during the attack phase compared with the intercritical phase; in the latter condition the visual reactivity to 27 Hz stimulus was increased over almost the entire scalp compared with normal subjects. The EEG abnormalities confirm a fluctuating modification of alpha activity during the **migraine** attack, probably related to a functional disorder. The suppression of visual reactivity during the **migraine** attack could be related to a phenomenon of neuronal depolarization such as **spreading** depression, occurring in a situation of central neuronal increased excitability predisposing to **migraine** attacks." [Abstract]

Aurora SK, Ahmad BK, Welch KM, Bhardhwaj P, Ramadan NM.

Transcranial magnetic stimulation confirms hyperexcitability of occipital cortex in migraine.

Neurology. 1998 Apr;50(4):1111-4.

"OBJECTIVES: We hypothesized that the hyperexcitability of occipital cortex neurons may predispose **migraine** subjects to develop **spreading** depression, the putative basis of **migraine** with aura (MwA). To date there is no direct physiologic correlate confirming this in patients. Accordingly, we evaluated the differences in the threshold of occipital cortex excitation between MwA patients and normal controls (C) using transcranial magnetic stimulation (TMS). METHODS: TMS was performed using the Cadwell MES 10 stimulator. A circular coil 9.5 cm in diameter was applied to the occipital scalp (7 cm above the inion). Stimulator intensity was increased in 10% increments until subjects reported visual phenomena or 100% intensity was reached. Stimulation intensity was then fine-tuned to determine the threshold at which phosphenes were just visualized. RESULTS: Eleven MwA patients, mean age 37 +/- 7 years, were compared with 11 C, mean age 37.7 +/- 7 years. The difference in the proportion of subjects with phosphene generation between MwA patients and C was significant (MwA patients 100% versus C 27.3%, p = 0.001). The mean threshold level for MwA patients was 44.2 +/- 8.6 versus 68.7 +/- 3.1 for C (p = 0.0001). All threshold levels for MwA patients were lower than the lowest threshold for C; the MwA patient with the lowest threshold had an aura after stimulation. CONCLUSIONS: The threshold for excitability of occipital cortex is lower in MwA patients compared with C. This is a direct neurophysiologic correlate for clinical observations that have indicated hyperexcitability of the occipital cortex in migraineurs." [Abstract]

Spierings EL.

Pathogenesis of the migraine attack.

Clin J Pain. 2003 Jul-Aug;19(4):255-62.

"BACKGROUND: There is clinical experimental evidence that extracranial arterial vasodilation, extracranial neurogenic inflammation, and decreased inhibition of central pain trigeminovascular system stimulates perivascular trigeminal sensory afferent nerves with release of vasoactive neuropeptides, resulting in vasodilation and transduction of central nociceptive information. There is then a relay of pain impulses to central second- and third-order neurons and activation of brain stem autonomic nuclei to induce associated symptoms." [Abstract]

Ramadan NM.

The link between glutamate and migraine.

CNS Spectr. 2003 Jun;8(6):446-9.

"**Migraine** pain-relay centers, including the trigeminal ganglion, trigeminal nucleus caudalis, and thalamus, contain glutamate-positive neurons, and glutamate activates the trigeminal nucleus caudalis. Glutamate is implicated in **cortical spreading** depression, trigeminovascular activation, and central sensitization. Glutamate receptor-subtype antagonists are effective in preclinical models of **migraine**, and in the clinic. These preclinical and clinical observations argue for a strong link between **migraine** and the glutamatergic system, a link that is important to further characterize in an effort to better understand **migraine** mechanisms and deliver effective therapies." [Abstract]

Gorji A, Scheller D, Straub H, Tegtmeier F, Kohling R, Hohling JM, Tuxhorn I, Ebner A, Wolf P, Werner Panneck H, Oppel F, Speckmann EJ.

Spreading depression in human neocortical slices.

Brain Res. 2001 Jul 6;906(1-2):74-83.

"**Cortical spreading** depression (CSD) occurrence has been suggested to be associated with seizures, **migraine** aura, head injury and brain ischemia-infarction. Only few studies identified CSD in human neocortical slices and no comprehensive study so far evaluated this phenomenon in human. Using the neocortical tissue excised for treatment of intractable epilepsy, we aimed to investigate CSD in human. CSD was induced by KCl injection and by modulating T-type Ca(2+) currents in incubated human neocortical tissues in an interphase mode. The DC-fluctuations were recorded by inserting microelectrodes into different **cortical** layers. Local injection of KCl triggered single CSD that propagated at 3.1+/-0.1 mm/min. Repetitive CSD also occurred spontaneously during long lasting application (5 h) of the T-type Ca(2+) channel blockers amiloride (50 microM) or NiCl(2) (10 microM) which was concomitant with a reversible extracellular potassium increase up to 50 mM. CSD could be blocked by the N-methyl-D-aspartate receptor antagonist 2-amino-5-phosphonovaleric acid in all cases. The results demonstrate that modulation of the Ca(2+) dynamics conditioned human neocortical slices and increased their susceptibility to generate CSD. Furthermore, these data indicate that glutamatergic pathway plays a role in CSD phenomenon in human." [Abstract]

McLachlan RS.

Suppression of spreading depression of Leao in neocortex by an N-methyl-D-aspartate receptor antagonist.

Can J Neurol Sci. 1992 Nov;19(4):487-91.
[Abstract]

Obrenovitch TP, Zilkha E.

Inhibition of cortical spreading depression by L-701,324, a novel antagonist at the glycine site of the N-methyl-D-aspartate receptor complex.

Br J Pharmacol. 1996 Mar;117(5):931-7. [Abstract]

transmission are involved in the pathogenesis of the **migraine** headache. The **migraine** aura is likely caused by a neurophysiologic phenomenon akin to Leao's **cortical spreading** depression, a wave of short-lasting neuronal excitation that travels over the cerebral cortex, followed by prolonged depression of **cortical** neuronal activity. METHOD: A concept of the pathogenesis of the **migraine** attack is presented, in which the relation of the mechanism of the **migraine** aura and that of the **migraine** headache is considered parallel rather than sequential in nature. CONCLUSIONS: The process driving the pathogenesis of the **migraine** attack and susceptible to the **migraine** trigger factors may be located in the brain stem." [Abstract]

Baron JC.

[The pathophysiology of migraine: insights from functional neuroimaging]

Rev Neurol (Paris). 2000;156 Suppl 4:4S15-23.

"Over the last 20 years, functional neuroimaging has led to major advances in the understanding of the pathophysiology of **migraine**. The **migraine** aura is characterized by the occurrence of an hypoperfusion of moderate intensity which is peculiar by its initial appearance in the posterior cortex and its anterior spread at a speed of about 2 to 3mm per minute, congruent with the migrainous march of neurologic deficit and reminiscent of the phenomenon of **cortical spreading** depression described in the laboratory animal after various neuronal aggressions. The hypoperfusion is followed by a phase of long-lasting hyperperfusion temporally dissociated from the headache, which seems rather to result from vasodilatation and inflammation of the extra-cerebral large vessels. Although this sequence of hypoperfusion followed by hyperperfusion would be consistent with an ischemic process, there is presently no formal argument in favour of such a process being operational in **migraine** aura. It is however possible that migrainous subjects are genetically susceptible to the development of some unknown process at the borderline between **spreading** depression and classic ischemia. In **migraine** without aura, the data indicate only rare and mild changes in brain perfusion, although there also exist isolated observations of pauci-symptomatic **spreading** bilateral hypoperfusion. Physiologic imaging has also documented the occurrence during **migraine** without aura of a dorsal mesencephalic activation in the vicinity of the raphe and the locus coeruleus, independent of the pain itself and which might represent the long sought-after "**migraine** generator". It remains unknown if this phenomenon is also present in **migraine** with aura. The main prevalent hypotheses attempting a synthesis of all the available data are briefly presented in the conclusion." [Abstract]

Kaube H, Knight YE, Storer RJ, Hoskin KL, May A, Goadsby PJ.

Vasodilator agents and supracollicular transection fail to inhibit cortical spreading depression in the cat.

Cephalalgia. 1999 Jul;19(6):592-7.

"It remains an open question as to whether **cortical spreading** depression (CSD) is the pathophysiological correlate of the neurological symptoms in **migraine** with aura. In the experimental animal, CSD is an electrophysiological phenomenon mainly mediated via NMDA receptors. However, according to case reports in humans, visual aura in **migraine** can be alleviated by vasodilator substances, such as

Lauritzen M.

Pathophysiology of the migraine aura. The spreading depression theory.

Brain. 1994 Feb;117 (Pt 1):199-210.

"The characteristic form and development of sensory disturbances during **migraine** auras suggests that the underlying mechanism is a disturbance of the cerebral cortex, probably the **cortical spreading** depression (CSD) of Leao. The demonstration of unique changes of brain blood flow during attacks of **migraine** with aura, which have been replicated in animal experiments during CSD, constitutes another important line of support for the '**spreading** depression' theory, which may be a key to an understanding of the **migraine** attack. **Cortical spreading** depression is a short-lasting depolarization wave that moves across the cortex at a rate of 3-5 mm/min. A brief phase of excitation heralds the reaction which is immediately followed by prolonged nerve cell depression synchronously with a dramatic failure of brain ion homeostasis, efflux of excitatory amino acids from nerve cells and enhanced energy metabolism. Recent experimental work has shown that CSD in the neocortex of a variety of species including man is dependent on activation of a single receptor, the N-methyl-D-aspartate receptor, one of the three subtypes of glutamate receptors. The combined experimental and clinical studies point to fruitful areas in which to look for **migraine** treatments of the future and provide a framework within which important aspects of the **migraine** attack can be modelled." [Abstract]

Choudhuri R, Cui L, Yong C, Bowyer S, Klein RM, Welch KM, Berman NE.

Cortical spreading depression and gene regulation: relevance to migraine.

Ann Neurol. 2002 Apr;51(4):499-506.

"**Cortical spreading** depression (CSD) may be the underlying mechanism of **migraine** aura. The role of CSD in initiating a **migraine** headache remains to be determined, but it might involve specific changes in gene expression in the brain. To examine these changes, four episodes of CSD at 5-minute intervals were induced in the mouse brain by application of 300mM KCl, and gene expression was examined 2 hours later using cDNA array and reverse transcriptase-polymerase chain reaction. Controls consisted of groups that received anesthesia only, attachment of recording electrodes only, and application of 0.9% NaCl. Of the over 1,180 genes examined in our experiments, those consistently regulated by CSD included vasoactive peptides; the vasodilator atrial natriuretic peptide was induced by CSD, while the vasoconstrictor neuropeptide Y was downregulated. Other genes specifically regulated by CSD were involved in oxidative stress responses (major prion protein, glutathione-S-transferase-5, and apolipoprotein E). L-type calcium channel mRNA was upregulated. In summary, CSD regulates genes that are intrinsic to its propagation, that identify accompanying vascular responses as a potential source of pain, and that protect against its potential pathological consequences. We believe these observations have strong relevance to the mechanisms of **migraine** and its outcomes." [Abstract]

Martins-Ferreira H, Nedergaard M, Nicholson C.

Perspectives on spreading depression.

Brain Res Brain Res Rev. 2000 Apr;32(1):215-34.

"**Spreading** depression (SD) consists of a transient suppression of all neuronal activity that spreads slowly across regions of gray matter. The paper is divided into three parts. Martins-Ferreira describes 30 years of research on SD in the isolated retina. Much

amyl nitrite and isoprenaline. There is also circumstantial evidence that brainstem nuclei (dorsal raphe nucleus and locus coeruleus) may play a pivotal role in the initiation of aura. In this study, CSD was elicited in alpha-chloralose anesthetized cats by **cortical** needle stab injury and monitored by means of laser Doppler flowmetry. Topical application of isoprenaline (0.1-1%) and amyl nitrite (0.05%) onto the exposed cortex had no effect on the elicitation or propagation of CSD. Also, after supracollicular transection, subsequent CSDs showed no differences in the speed of propagation and associated flow changes. We conclude from these data that--given CSD probably exists in humans during **migraine--spreading** neurological deficits during **migraine** aura are independent of brainstem influence and have a primarily neuronal rather than vascular mechanism of generation." [Abstract]

Ingvardsen BK, Laursen H, Olsen UB, Hansen AJ.

Possible mechanism of c-fos expression in trigeminal nucleus caudalis following cortical spreading depression.

Pain. 1997 Sep;72(3):407-15.

"**Cortical spreading** depression (CSD) is characterized by a transient, reversible depression of EEG activity which advances across the **cortical** surface at a velocity of 2-5 mm/min. CSD was originally linked to the aura phase of **migraine**, but recently also to **migraine** headache. The theory is that CSD activates meningeal trigeminal C-fibers causing neurogenic inflammation and pain (Moskowitz, M.A., Nozaki, K. and Kraig, R.P., Neocortical **spreading** depression provokes the expression of c-fos protein-like immunoreactivity within trigeminal nucleus caudalis via trigeminovascular mechanisms, J. Neurosci., 13 (1993) 1167-1177). The present study is an examination of the proposed link between CSD elicited in rats and activation of trigeminal nerve fibers. Multiple CSDs were elicited unilaterally for 1 h by KCl injections (1 M, 5 microliters) into the right hemisphere, while NaCl (1 M, 5 microliters) was injected into the left as control. After an additional 1 h the animals were sacrificed and trigeminal activation assessed by the expression of c-fos in trigeminal nucleus caudalis (TNC) using immunohistochemistry. The correlation between the number of CSDs and the extent of c-fos expression was determined. In addition the effect of sumatriptan (0.3 mg/kg) and morphine (3 mg/kg) given i.v. 30 min before elicitation of CSD was evaluated. CSD caused increased c-fos expression in lamina I and II of TNC where C-fibers, end, the response being greater ipsilaterally. Morphine, but not sumatriptan, reduced c-fos expression in both the ipsilateral and contralateral TNC by 71% ($P < 0.05$ and $P = 0.19$, respectively), confirming that nociceptors have been activated. No positive correlation was seen between the number of CSDs and the extent of c-fos expression in TNC. Instead we observed a positive, linear correlation between the number of KCl injections and the extent of c-fos expression in TNC (correlation coefficient $r = 0.709$, $P < 0.05$). We suggest that the C-fiber activation observed is caused by hyperosmolar KCl/NaCl and not CSD. Hence, our results do not support the hypothesis of Moskowitz et al. (Moskowitz, M.A., Nozaki, K. and Kraig, R.P., Neocortical **spreading** depression provokes the expression of c-fos protein-like immunoreactivity within trigeminal nucleus caudalis via trigeminovascular mechanisms, J. Neurosci., 13 (1993) 1167-1177) which links CSD with **migraine** headache." [Abstract]

of this work has relied on the prominent intrinsic optical signals that accompany SD in the retina. By inducing SD to propagate in circles with a velocity of 3.7 mm min(-1), it is possible to investigate the finely balanced electrochemical equilibrium that maintains the traveling wave. SD is accompanied by a slow negative extracellular voltage and ion movements that are greatest in the inner plexiform layer of the retina. Nedergaard discusses the role of astrocytes in SD propagation. Astrocytes mediate slowly moving waves of intracellular Ca(2+) increase, for which gap junctions are essential. SD is accompanied by entry of Ca(2+) into cells and fails when gap junctions are blocked. SD, however, is blocked by glutamate receptor antagonists but glial Ca(2+) waves are not. Astrocytic Ca(2+) waves are probably involved in the initiation of SD but other factors, including K(+), glutamate and purinergic receptors, are necessary for sustained propagation. Nicholson describes studies on the different preparations that helped clarify the role of extracellular space in SD. It has long been known that extracellular K(+) reaches levels of 50 mM or more during SD. Studies with ion-selective microelectrodes showed that extracellular Na(+) and Cl(-) fall by as much as 100 mM during SD, and water leaves the extracellular space. Further work showed that extracellular Ca(2+) falls 10-fold during SD and significant changes in extracellular pH and ascorbate occur. These studies imply that large perturbations of the extracellular milieu occur during SD and are an essential part of the interlocking cascade of events that produce this still mysterious phenomenon." [Abstract]

Gold L, Back T, Arnold G, Dreier J, Einhaupl KM, Reuter U, Dirnagl U.

Cortical spreading depression-associated hyperemia in rats: involvement of serotonin.

Brain Res. 1998 Feb 9;783(2):188-93.

"We investigated whether the vasoactive neurotransmitter serotonin (5-HT) is involved in **cortical spreading** depression (CSD)-associated hyperemia in the rat. We focused on the 5-HT2 receptor, which is engaged in 5-HT induced small arteriolar relaxation in cats, as well as on the 5-HT1D/1B receptor, the binding site of the potent antimigraine drug sumatriptan. In male barbiturate anaesthetized Wistar rats (n=25) CSDs were elicited by brain topical application of 1 M KCl, and the DC-potential and regional cerebral blood flow (rCBF, by Laser Doppler flowmetry) were measured over the same hemisphere through dura and thinned bone, respectively. Intravenous application of 8 mg/kg of the 5-HT2A/2C receptor antagonist ritanserin (group I; n=8) significantly reduced the hyperperfusion amplitude during CSD by approximately 44% ($p<0.05$, from 342+/-124 to 194+/-97%, baseline before CSD=100%), and prolonged its duration by approx. 30%. Vehicle alone (group II; n=4) did not affect CSD hyperperfusion. The highly selective 5-HT1D/1B receptor agonist 311C90 was given in two doses: 100 micrograms/kg i.v. (n=5) had no effect on CSD hyperperfusion, while 800 micrograms/kg (n=5) increased hyperperfusion significantly ($p<0.05$, from 224+/-86 to 310+/-148%). We conclude that serotonin is, probably via 5-HT2 receptors, involved in the modulation of the regional cerebral blood flow increase during CSD. Novel highly selective receptor antagonists may help to discriminate the differential contribution of various 5-HT receptor subspecies." [Abstract]

Osten P, Hrabetova S, Sacktor TC.

Differential downregulation of protein kinase C isoforms in spreading depression.

Neurosci Lett. 1996 Dec 27;221(1):37-40.

Moskowitz MA, Nozaki K, Kraig RP.

Neocortical spreading depression provokes the expression of c-fos protein-like immunoreactivity within trigeminal nucleus caudalis via trigeminovascular mechanisms.

J Neurosci. 1993 Mar;13(3):1167-77.

"The effects of neocortical **spreading** depression (SD) on the expression of immunoreactive c-fos protein were examined within the superficial laminae of trigeminal nucleus caudalis (TNC), a brainstem region processing nociceptive information. KCl was microinjected into the left parietal cortex at 9 min intervals over 1 hr, and SD was detected by a shift in interstitial DC potential within adjacent frontal cortex. The stained cells in lower brainstem and upper cervical spinal cord were counted on both sides after tissues were sectioned (50 microns) and processed for c-fos protein-like immunoreactivity (LI) using a rabbit polyclonal antiserum. C-fos protein-LI was visualized in the ventrolateral TNC, chiefly in laminae I and IIo and predominantly within spinal segment C1-2 (e.g., -1.5 to -4.5 mm from obex) ipsilaterally. SD significantly increased cell staining within ipsilateral TNC. The ratio of cells in laminae I and IIo on the left: right sides was 1.32 +/- 0.13 after 1 M KCl, as compared to 1.06 +/- 0.05 in control animals receiving 1 M NaCl instead of KCl microinjections ($p < 0.01$). The ratio was reduced to an insignificant difference after chronic surgical transection of meningeal afferents and recurrent SD (1.09 +/- 0.11). Pretreatment with intravenous sumatriptan, a 5-HT1-like receptor agonist that selectively blocks meningeal C-fibers and attenuates c-fos protein-LI within TNC after noxious meningeal stimulation, also reduced the ratio to an insignificant difference (1.10 +/- 0.09). Sumatriptan or chronic surgical transection of meningeal afferents, however, did not reduce the ability of KCl microinjections to induce SD. On the other hand, combined hyperoxia and hypercapnia not only reduced the number of evoked SDs from 6.3 +/- 1.0 to 2.5 +/- 1.2 after 0.15 M KCl microinjection, but also significantly ($p < 0.01$) reduced associated c-fos protein-LI in TNC. These data indicate that multiple neocortical SDs activate cells within TNC. The increase in c-fos protein-LI, observed predominantly ipsilaterally, was probably mediated by SD-induced stimulation of ipsilaterally projecting unmyelinated C-fibers innervating the meninges. If true, this is the first report demonstrating that neurophysiological events within cerebral cortex can activate brainstem regions involved in the processing of nociceptive information via trigeminovascular mechanisms." [Abstract]

Gorji A.

Spreading depression: a review of the clinical relevance.

Brain Res Brain Res Rev. 2001 Dec;38(1-2):33-60. [Abstract]

Lauritzen M.

Cortical spreading depression in migraine.

Cephalalgia. 2001 Sep;21(7):757-60. [Abstract]

Wiedemann M, de Lima VM, Hanke W.

Effects of antimigraine drugs on retinal spreading depression.

Naunyn Schmiedebergs Arch Pharmacol. 1996 Apr;353 (5):552-6.

"It has been suggested that **spreading** depression may play a

"**Spreading** depression (SD) is a propagating depolarization of populations of neurons induced by intense electrical, chemical, or mechanical stimulation, which has been proposed to be an important mechanism in the aura of **migraine**. SD is characterized by a transient loss of synaptic transmission and thus may involve signal transduction mechanisms known to modulate synaptic strength. To examine the underlying pathophysiological molecular mechanisms of SD, we analyzed the regulation of eight protein kinase C (PKC) isoforms by immunoblot during SD induced by a high-intensity stimulus of synaptic afferents in the CA1 region of hippocampal slices. We observed a downregulation of the conventional (alpha, beta I, beta II, gamma) and the novel (delta, epsilon, eta) PKC isoforms in SD, but no change in the atypical isozyme (zeta). The coordinate downregulation of multiple PKC isoforms may be important in the functional depression of neuronal activity in SD. In contrast, the atypical zeta, and its constitutively active fragment PKM zeta, is a specific PKC isozyme that has been implicated in the maintenance of long-term potentiation (LTP) and long-term depression (LTD), widely studied models for the mechanism of memory. The stability of PKC zeta and PKM zeta in SD indicates that a molecular mechanism for the maintenance of LTP/ LTD is relatively resistant to alterations that occur during pathophysiologically large ionic fluxes. This result could help to explain the retention of information stored in the cortex despite the massive release of excitatory neurotransmitter and neuronal depolarization that may occur during the migrainous aura." [Abstract]

Mitsikostas DD, Sanchez del Rio M.

Receptor systems mediating c-fos expression within trigeminal nucleus caudalis in animal models of migraine.

Brain Res Brain Res Rev. 2001 Mar;35(1):20-35.

"In intracranial structures unmyelinated C- and Adelta-fibers of the trigeminal nerve transmit pain stimuli from meninges to the trigeminal nucleus caudalis (Sp5C). Peripheral nerve endings surround meningeal vessels (the so-called trigeminovascular system) and contain vasoactive neuropeptides (calcitonin gene-related peptide, substance P and neurokinin A). Activation of the trigeminovascular system promotes a meningeal sterile inflammatory response through the release of neuropeptides by peripheral endings. Orthodromic conduction along trigeminovascular fibers transmits information centrally with induction of immediate early c-fos gene within post-synaptic Sp5C neurons, as a marker of neuronal activity within central nociceptive pathways. In laboratory animals the system is activated by either electrical stimulation of the TG, chemical stimulation of the meninges, electrical or mechanical stimulation of the superior sagittal sinus or by induction of **cortical spreading** depression. All these techniques induce c-fos within Sp5C and are used as a rodent/feline model of vascular headache in humans. Up-to-date there is evidence that at least ten receptors (5-HT(1B), 5-HT(1D), 5-HT(lF), 5-HT(2B), NK-1, GABA(A), NMDA, AMPA, class III metabotropic glutamate receptors, and opioids mu receptors) modulate c-fos expression within Sp5C. These receptors represent potential targets for anti-**migraine** drugs as shown by triptans (5-HT(1B/1D/1F)) and ergot alkaloids (5-HT(1A1B/1D/1F)). This review discusses the importance of c-fos expression within Sp5C as a marker of cephalic nociception, the different cephalic pain models that induce c-fos within Sp5C, the receptors involved and their potential role as targets for anti-**migraine** drugs." [Abstract]

role in triggering classical **migraine**. In this study the retinal **spreading** depression was used as a pharmacological tool to test the neuronal effects of several common antimigraine drugs. As the chicken retina is void of any blood vessels the observed effects must be of pure neuronal origin. It is shown that propranolol, sumatriptan, methysergide, paracetamol and acetylsalicyclic acid decrease the propagation velocity of retinal **spreading** depression waves, accelerate the recovery of the optical and electrical signal and reduce the amplitude of the negative potential shift, concomitant with the **spreading** depression. Barbiturate increases the **spreading** velocity, and the amplitude of the potential shift. Ergotamine, clonidine, lisuride and iprazochrome have no significant influence on retinal **spreading** depression." [Abstract]

Brand S, Fernandes de Lima VM, Hanke W.

Pharmacological modulation of the refractory period of retinal spreading depression.

Naunyn Schmiedebergs Arch Pharmacol. 1998 Apr;357 (4):419-25. [Abstract]

Read SJ, Parsons AA.

Sumatriptan modifies cortical free radical release during cortical spreading depression. A novel antimigraine action for sumatriptan?

Brain Res. 2000 Jul 7;870(1-2):44-53.

"Increases in concentration of brain NO are proposed to initiate and mediate **migraine** headache. Triggered by focal depolarisation, **spreading** depression (SD) represents a suitable mechanism for eliciting widespread release of nitric oxide. The current study examines the effect of sumatriptan, a 5-HT(1B/1D) agonist and effective antimigraine therapy, on free radical release (nitric oxide and superoxide) in SD in the simple and complex cortices of the rat and cat. Following initiation of SD, sumatriptan pretreatment (300 microg kg(-1) i.v., 15 min prior to SD) modulated all phases of nitric oxide release associated with each SD in both cats and rats. As a result, superoxide levels were observed to significantly (ANOVA, post hoc LSD) increase versus vehicle treated animals (saline 1 ml kg(-1) i.v. 15 min prior to SD) during specific phases of each SD depolarisation. Averaged over all SD depolarisations, mean peak SD nitric oxide levels per depolarisation were 0.73+/-0.23 microM (n=29) in cats, and 0.42+/-0.09 microM (n=34) in rats. Sumatriptan significantly (Students t-test, P<0.05, two tailed hypothesis, P<0.05) modulated this increase in **cortical** nitric oxide concentrations to 0.32+/-0.06 microM (n=25) and 0. 22+/-0.07 microM (n=37) in cats and rats. Sumatriptan appears to decrease the amplitude of nitric oxide release but enhances extracellular superoxide concentrations in both lissencephalic and gyrencephalic cortices during SD." [Abstract]

Bradley DP, Smith MI, Netsiri C, Smith JM, Bockhorst KH, Hall LD, Huang CL, Leslie RA, Parsons AA, James MF.

Diffusion-weighted MRI used to detect in vivo modulation of cortical spreading depression: comparison of sumatriptan and tonabersat.

Exp Neurol. 2001 Dec;172(2):342-53.

"**Spreading cortical** depolarization and depression of electroencephalographic activity (SD) may underlie the aura and **spreading** neurovascular events of **migraine**. **Cortical** depolarization may also precipitate the progressive development of cerebral pathology following ischemia.

Yokota C, Kuge Y, Hasegawa Y, Tagaya M, Abumiya T, Ejima N, Tamaki N, Yamaguchi T, Minematsu K.

Unique profile of spreading depression in a primate model.

J Cereb Blood Flow Metab. 2002 Jul;22(7):835-42.

"**Spreading** depression (SD) is considered to play a role in pathologic conditions of humans such as in the evolution of ischemic brain injury and **migraine** aura. Because many studies have demonstrated **spreading** hypoperfusion in patients with **migraine** and persistent hypoperfusion in nonprimate animal models of SD, these changes in cerebral blood flow (CBF) were regarded as an epiphenomenon of SD. However, there is no direct evidence of the occurrence of SD in primates. The authors attempted to elicit SD by applying 3.3 mol/L potassium chloride to the cerebral cortex of nine male cynomolgus monkeys. The CBF was monitored by positron emission tomography in five animals. Propagated direct-current shifts were found by the two neighboring microelectrodes only in one animal. The direct-current wave propagated at a speed of 4 mm/min and its amplitude was 20 mV, being consistent with the SD findings. Except in one animal with 6 SD episodes, SD waves were recorded infrequently at the rostral site (none in three animals, once in three, and twice in two). Focal hyperemia accompanied SD. Neither **spreading** hypoperfusion nor persistent hypoperfusion was found. These unique features of SD in primates raise a doubt as to whether the role of SD in nonprimate animals is the same as that in stroke and **migraine** in humans." [Abstract]

Ba AM, Guiou M, Pouratian N, Muthialu A, Rex DE, Cannestra AF, Chen JW, Toga AW.

Multiwavelength optical intrinsic signal imaging of cortical spreading depression.

J Neurophysiol. 2002 Nov;88(5):2726-35.

"**Cortical spreading** depression (CSD) is an important disease model for **migraine** and cerebral ischemia. In this study, we exploit the high temporal and spatial resolution of optical imaging to characterize perfusion-dependent and -independent changes in response to CSD and to investigate the etiology of reflectance changes during CSD. In this experiment, we characterized the optical response to CSD at wavelengths that emphasize perfusion-related changes (610 and 550 nm), and we compared these results with 850 nm and blood volume data. Blood volume changes during CSD were recorded using an intravascular fluorescent dye, Texas Red dextran. We observed triphasic optical signals at 850 and 550 nm characterized by **spreading** waves of increased, decreased, then increased reflectance (Fig. 1) which expanded at a rate of approximately 3-5 mm/min. The signal at 610 nm had a similar initial phase, but the phase 2 response was slightly more complex, with a parenchymal decrease in reflectance but a vascular increase in reflectance. Reflectance values decreased in phase three. Blood volume signals were delayed relative to the optical intrinsic signals and corresponded temporally to phases 2 and 3. This is the first study to characterize optical imaging of intrinsic signal responses to CSD, in vivo, at multiple wavelengths. The data presented here suggest that changes in light scattering precede perfusion responses, the blood volume increase (phase 2) is accompanied by a reduction in deoxyhemoglobin, and the blood volume decrease (phase 3) is accompanied by an increase in deoxyhemoglobin. Previous studies have suggested the oligemia of **spreading** depression was a result of decreased metabolic demand. This study suggests that during the oligemic period there is a greater reduction in oxygen delivery than in demand." [Abstract]

However, data on SD in the human brain are sparse, most likely reflecting the technical difficulties involved in performing such clinical studies. We have previously shown that the transient cerebral water disturbances during SD can be quantitatively investigated in the gyrencephalic brain using repetitive diffusion-weighted magnetic resonance imaging (DWI). To investigate whether DWI could detect modulation of the spatiotemporal properties of SD in vivo, the effects of the antimigraine drug sumatriptan (0.3 mg/kg iv) and the novel anticonvulsant tonabersat (10 mg/kg ip) were evaluated in the cat brain. Supporting previous findings, sumatriptan did not affect the numbers of events (range, 4-8), the duration of SD activity (39.8 +/- 4.4 min, mean +/- SEM), and event velocity (2.2 +/- 0.4 mm min(-1)); tonabersat significantly reduced SD event initiation (range, 0-3) and duration (13.2 +/- 5.0 min) and increased primary event velocity (5.4 +/- 0.7 mm min(-1)). However, both drugs significantly decreased, by >50%, the spatial extent of the first KCl-evoked SD event, and sumatriptan significantly increased event propagation across the suprasylvian sulcus (5.5 +/- 0.6 vs 2.4 +/- 0.4 events in controls). These results demonstrate (1) the feasibility of using DWI to evaluate therapeutic effects on SD, and (2) that sumatriptan may directly modulate the spatial distribution of SD activity in the gyrencephalic brain." [Abstract]

Read SJ, Hirst WD, Upton N, Parsons AA.

Cortical spreading depression produces increased cGMP levels in cortex and brain stem that is inhibited by tonabersat (SB-220453) but not sumatriptan.

Brain Res. 2001 Feb 9;891(1-2):69-77.

"**Migraine** headache is proposed to be mediated by nitric oxide (NO). Suitable mechanisms for eliciting increases in brain NO concentration in migraineurs have not yet been identified, although, animal models highlight **cortical spreading** depression (CSD) as a potential candidate. These studies have focused on CSD-associated NO release at highly acute time points (min-hours) and have not employed markers of NO metabolism with direct clinical application e.g. cGMP. The current study evaluated changes in plasma cGMP concentrations 3 h, 24 h and 3 days post-CSD and compared these to **cortical** and brainstem cGMP concentrations at 3 days. Moreover, this study also examined the effect of sumatriptan, a clinically effective antimigraine agent, and tonabersat (SB-220453) a potential novel antimigraine agent, on any observed changes in cGMP. Following pre-treatment with vehicle (n=3), sumatriptan (300 microg kg(-1) i.v, n=3) or tonabersat (SB-220453 10 mg kg(-1) i.p., n=3), CSD was evoked in anaesthetised rats by a 6-min KCl application to the parietal cortex. In the vehicle-treated group a median of eight depolarisations, were observed. Sumatriptan had no effect on the number of depolarisations, whereas tonabersat significantly reduced the number of events (median=2). No depolarisation events were observed throughout the recording period in the sham group. Following KCl application plasma cGMP concentrations were reduced up to 24 h post-CSD, but not significantly different from sham animals at 3 days. CSD in vehicle-treated animals produced a highly significant elevation in cGMP concentration in the brain stem 3 days after application of KCl. cGMP concentration increased 2.3-fold from 68+/-8 fmol/mg in sham animals (n=3) to 158+/-28 fmol/mg in the vehicle group. This increase in brain stem cGMP was abolished by tonabersat pre-treatment but not by sumatriptan." [Abstract]

Oleg V. Godukhin, and Tihomir P. Obrenovitch

Asymmetric Propagation of Spreading Depression Along the Anteroposterior Axis of the Cerebral Cortex in Mice

J Neurophysiol 86: 2109-2111, 2001.

"The purpose of this study was to ascertain whether or not **spreading** depression (CSD) propagates symmetrically along the anteroposterior axis of the cortex of mice, and to determine where CSD should be elicited to achieve a uniform exposure of the cortex to this phenomenon. Experiments were performed in halothane-anesthetized mice, with three different locations aligned 1.5 mm from the midline used for either KCl elicitation of CSD or the recording of its propagation. Our results demonstrated that, at least in the mouse cortex, CSD propagated much more effectively from posterior to anterior regions than in the opposite direction. This feature was due to a different efficacy of propagation in the two opposite directions, and not to a reduced susceptibility of occipital regions to CSD elicitation. Heterogeneous CSD propagation constitutes a potential pitfall for neurochemical studies of post-CSD changes in mice, as brain tissue samples collected for this purpose should be uniformly exposed to CSD. Occipital sites for CSD induction are clearly optimal for this purpose. If CSD propagation is confirmed to be more effective from posterior to anterior regions in other species, this may be relevant to the pathophysiology of classical **migraine** because the most frequent aura symptoms (i.e., visual disturbances) originate in the occipital cortex." [Full Text]

Shimazawa M, Hara H.

An experimental model of migraine with aura: cortical hypoperfusion following spreading depression in the awake and freely moving rat.

Clin Exp Pharmacol Physiol. 1996 Oct-Nov;23(10-11):890-2.

"1. **Cortical spreading** depression (CSD) was induced by direct current stimulation of the lateral frontal cortex in awake and freely moving rats. 2. Regional cerebral blood flow (rCBF) was continuously measured by a laser Doppler flowmeter using an acrylic cup which was chronically fixed on the surface of the cerebral cortex. Under the resting condition rCBF remained constant throughout the observation period and showed a high reproducibility. 3. rCBF increased to approximately 190% of control values during 1-3 min after CSD, and decreased to approximately 80% of control values, before returning to normal values 60 min after CSD. 4. These results are consistent with those found in anesthetized animals. This is the first study which has continuously monitored **cortical** hypoperfusion after CSD in awake and freely moving rats. The model is a useful system for studying **migraine** with aura." [Abstract]

Cui Y, Kataoka Y, Li QH, Yokoyama C, Yamagata A, Mochizuki-Oda N, Watanabe J, Yamada H, Watanabe Y.

Targeted tissue oxidation in the cerebral cortex induces local prolonged depolarization and cortical spreading depression in the rat brain.

Biochem Biophys Res Commun. 2003 Jan 17;300(3):631-6.

"**Spreading** depression (SD) has been linked to several neurological disorders as epilepsy, **migraine** aura, trauma, and cerebral ischemia, which were also influenced by disorderliness of the brain redox homeostasis. To investigate whether local tissue oxidation directly induces SD, we oxidized a restricted local area of the rat cerebral cortex using photo-dynamic tissue oxidation (PDTO) technique and examined the cerebral blood flow (CBF) and direct current (DC) potential in and around the

Wang M, Urenjak J, Fedele E, Obrenovitch TP.
Effects of phosphodiesterase inhibition on cortical spreading depression and associated changes in extracellular cyclic GMP.
Biochem Pharmacol. 2004 Apr 15;67(8):1619-27.
"**Cortical spreading** depression (CSD) is a temporary disruption of local ionic homeostasis that propagates slowly across the cerebral cortex, and may contribute to the pathophysiology of stroke and **migraine**. Previous studies demonstrated that nitric oxide (NO) formation promotes the repolarisation phase of CSD, and this effect may be cyclic GMP (cGMP)-mediated. Here, we have examined how phosphodiesterase (PDE) inhibition, either alone or superimposed on NO synthase (NOS) inhibition, alters CSD and the associated changes in extracellular cGMP. Microdialysis probes incorporating an electrode were implanted into the frontoparietal cortex of anaesthetised rats for quantitative recording of CSD, pharmacological manipulations, and dialysate sampling for cGMP measurements. CSD was induced by cathodal electrical stimulation in the region under study by microdialysis. Extracellular cGMP increased, but only slightly, during CSD. Perfusion of either zaprinast or sildenafil through the microdialysis probe, at concentrations that inhibited both PDE5 and PDE9 (and possibly other PDE), increased significantly extracellular cGMP. Unexpectedly, these levels remained high when NOS was subsequently inhibited with N (omega)-nitro-l-arginine methyl ester hydrochloride (l-NAME, 1mM). The most interesting pharmacological effect on CSD was obtained with sildenafil. This drug altered neither CSD nor the subsequent characteristic effect of NOS inhibition, i.e. a marked widening of CSD. The fact that NOS inhibition still widened CSD in the presence of the high extracellular levels of cGMP associated with PDE inhibition, suggests that NO may promote CSD recovery, independently of cGMP formation." [Abstract]

Smith MI, Read SJ, Chan WN, Thompson M, Hunter AJ, Upton N, Parsons AA.
Repetitive cortical spreading depression in a gyrencephalic feline brain: inhibition by the novel benzoylamino-benzopyran SB-220453.
Cephalalgia. 2000 Jul;20(6):546-53.
"Transient **cortical** depolarization is implicated in the pathology of **migraine**. SB-220453 is a potent anti-convulsant which inhibits neurogenic inflammation and **cortical spreading** depression (SD)-evoked nitric oxide release via a novel but unknown mechanism. This study further investigates the effects of SB-220453 on generation and propagation of repetitive SD in the anaesthetized cat. Vehicle or SB-220453 1, 3 or 10 mg/kg was administered intraperitoneally 90 min prior to induction of SD in the suprasylvian gyrus (SG). Changes in d.c. potential were recorded in the SG and the adjacent marginal gyrus (MG). In vehicle-treated animals (n = 7), a brief exposure (6 min) to KCl induced a median (25-75% range) number of five (four to six) and three (two to four) depolarizations over a duration of 55 min (32-59 min) and 51 min (34-58 min) in the SG and MG, respectively. SB-220453 produced dose-related inhibition of the number of events and period of repetitive SD activity. SB-220453 also reduced SD-induced repetitive pial vasodilatation but had no effect on resting haemodynamics. However, when SD events were observed in the presence of SB-220453, it had no effect on metabolic coupling. These oxidized area. Intensive PDTO induced prolonged depolarization only in the photo-oxidized area, which led to global changes of CBF and DC potential: synchronous negative shifts of DC potential (with an amplitude of approximately 20 mV) and hyperperfusion of CBF occurred. The changes in DC potential and CBF spread at a rate of around 3mm/min beyond the oxidized area to the whole hemisphere of the cerebral cortex, indicating that intensive local oxidation induces SD in the rat brain." [Abstract]

Anderson TR, Andrew RD.
Spreading depression: imaging and blockade in the rat neocortical brain slice.
J Neurophysiol. 2002 Nov;88(5):2713-25.
"**Spreading** depression (SD) is a profound but transient depolarization of neurons and glia that migrates across the **cortical** and subcortical gray at 2-5 mm/min. Under normoxic conditions, SD occurs during **migraine** aura where it precedes **migraine** pain but does not damage tissue. During stroke and head trauma, however, SD can arise repeatedly near the site of injury and may promote neuronal damage. We developed a superfused brain slice preparation that can repeatedly support robust SD during imaging and electrophysiological recording to test drugs that may block SD. Submerged rat neocortical slices were briefly exposed to artificial cerebrospinal fluid (ACSF) with KCl elevated to 26 mM. SD was evoked within 2 min, recorded in layers II/III both as a negative DC shift and as a propagating front of elevated light transmittance (LT) representing transient cell swelling in all **cortical** layers. An SD episode was initiated focally and could be repeatedly evoked and imaged with no damage to slices. As reported in vivo, pretreatment with one of several N-methyl-D-aspartate (NMDA) receptor antagonists blocked SD, but a non-NMDA glutamate receptor antagonist (CNQX) had no effect. NMDA receptor (NMDAR) activation does not initiate SD nor are NMDAR antagonists tolerated therapeutically so we searched for more efficacious drugs to block SD generation. Pretreatment with the sigma-one receptor (sigma(1)R) agonists dextromethorphan (10-100 microM), carbetapentane (100 microM), or 4-IBP (30 microM) blocked SD, even when KCl exposure was extended beyond 5 min. The block was independent of NMDA receptor antagonism. Two sigma(1)R antagonists [(+)-3PPP and BD-1063] removed this block but had no effect upon SD alone. Remarkably, the sigma(1) R agonists also substantially reduced general cell swelling evoked by bath application of 26 mM KCl. More potent sigma(1) R ligands that are therapeutically tolerated could prove useful in reducing SD associated with **migraine** and be of potential use in stroke or head trauma." [Abstract]

Fabricius M, Lauritzen M.
Transient hyperemia succeeds oligemia in the wake of cortical spreading depression.
Brain Res. 1993 Feb 5;602(2):350-3.
"Regional cerebral blood flow (rCBF) was examined following single episodes of **cortical spreading** depression (CSD) in rat brain after an intravenous bolus injection of [14C]iodoantipyrine. **Cortical** rCBF decreased to approximately 75% of control values during the first 60 min after CSD. This change was succeeded at 90-105 min by a small, transient flow increase. rCBF returned to normal at 120 min after CSD, and remained normal for the following 2 h. The same sequence of rCBF changes has been recorded in patients during **migraine** attacks. This study therefore supports the notion that CSD may serve as an animal model of **migraine**." [Abstract]

results show that SB-220453 produces marked inhibition of repetitive SD in the anaesthetized cat. SB-220453 may therefore have therapeutic potential in treatment of SD-like activity in **migraine**." [Abstract]

Read SJ, Smith MI, Hunter AJ, Upton N, Parsons AA.

SB-220453, a potential novel antimigraine agent, inhibits nitric oxide release following induction of cortical spreading depression in the anaesthetized cat.

Cephalalgia. 2000 Mar;20(2):92-9.

"Profound nitric oxide release associated with **cortical spreading** depression (SD), has been implicated in stroke, traumatic brain injury and **migraine** pathophysiology. SB-220453 represents a mechanistically novel, well-tolerated class of compounds which may have therapeutic potential in the treatment of conditions associated with neuronal hyperexcitability and inflammation. The aim of the present study was to investigate the effects of SB-220453 on the nitric oxide (NO) release associated with SD in the anaesthetized cat. In vehicle treated animals, KCl application for 6 min to the **cortical** suface produced repeated changes in extracellular direct current field potential with associated NO release. This activity was sustained for a median duration of 55 min (25-75% range, 32-59 min) and 59 min (25-75% range, 34-59 min), respectively. SB-220453 (1, 3 and 10 mg/kg i.p.) produced a dose-related inhibition of this activity and at the highest dose tested, the median duration of changes in extracellular field potential and NO release were reduced to 4 min (25-75% range, 4-5 min) and 5 min (25-75% range, 5-5 min), respectively. No effect was observed on basal systemic haemodynamic parameters or resting cerebral laser Doppler blood flux at any of the doses of SB-220453 tested. SB-220453 therefore represents a novel compound to assess the potential benefit of inhibiting SD associated nitric oxide release in neurological disease." [Abstract]

MaassenVanDenBrink A, van den Broek RW, de Vries R, Upton N, Parsons AA, Saxena PR.

The potential anti-migraine compound SB-220453 does not contract human isolated blood vessels or myocardium; a comparison with sumatriptan.

Cephalalgia. 2000 Jul;20(6):538-45. [Abstract]

Hara H, Shimazawa M, Hashimoto M, Sukamoto T.

[Anti-migraine effects of lomerizine]

Nippon Yakurigaku Zasshi. 1998 Oct;112 Suppl 1:138P-142P.

"Lomerizine, a novel Ca2+ channel blocker, is under development as an anti-**migraine** drug. We examined the effects on **spreading** depression (SD) induced by a brief period of hypoxia (40 to 60 sec) in rat hippocampal slices, the **cortical** hypoperfusion and **cortical** c-Fos-like immunoreactivity that follow KCl-induced SD in anesthetized rats as compared with those of flunarizine. Extracellular recording was made from the CA1 subfield. The latency of initiated SD was examined. Lomerizine (1 and 10 nM) and flunarizine (1 microM) significantly prolonged the latency in a concentration-dependent manner. After KCl application to the cortex, cerebral blood flow monitored by the laser Doppler flowmetry was approximately 20 to 30% below baseline for at least 60 min. Lomerizine (0.3 and 1 mg/kg, i.v.) and flunarizine (1 and 3 mg/kg, i.v.) administered 5 min before

Mraovitch S, Calando Y, Goadsby PJ, Seylaz J.

Subcortical cerebral blood flow and metabolic changes elicited by cortical spreading depression in rat.

Cephalalgia. 1992 Jun;12(3):137-41; discussion 127.

"Changes in cerebral **cortical** perfusion (CBFLDF), local cerebral blood flow (lCBF) and local cerebral glucose utilization (lCGU) elicited by unilateral **cortical spreading** depression (SD) were monitored and measured in separate groups of rats anesthetized with alpha-chloralose. CBFLDF was recorded with laser Doppler flowmetry, while lCBF and lCGU were measured by the quantitative autoradiographic [14C]iodoantipyrine and [14C]-2-deoxyglucose methods, respectively. SD elicited a wave of hyperemia after a latency of 2 to 3 min followed by an oligemic phase. Ninety minutes following the onset of SD **cortical** (frontal, parietal and occipital) lCBF and lCGU were essentially the same as on the contralateral side and in sham-treated rats. However, alteration in the lCBF and lCGU in upper and lower brainstem persisted. The present results demonstrate, for the first time, that long-lasting cerebrovascular and metabolic alterations take place within the subcortical regions following SD." [Abstract]

Lacombe P, Sercombe R, Correze JL, Springhetti V, Seylaz J.

Spreading depression induces prolonged reduction of cortical blood flow reactivity in the rat.

Exp Neurol. 1992 Sep;117(3):278-86.

"The purpose of the present study was to examine the dynamic aspects of the cerebrovascular events occurring during and up to 2 h following **cortical spreading** depression (CSD) in the rat, using the mass spectrometry technique which enables continuous measurements of the **cortical** tissue PO2 and PCO2 and repeated blood flow measurements (CoBF) by helium clearance. We mostly sought to determine whether **cortical** perforation by a stimulation electrode induced long-lasting perturbation of the **cortical** vasoreactivity to hypercapnia and basal forebrain electrical stimulation. **Cortical** perforation in the animal under alpha-chloralose anesthesia, chronically implanted with mass spectrometry probes, was associated with biphasic changes in tissue gases. PO2 first briefly decreased (-7.8%) and then strongly increased (+79%) while PCO2 changed in the opposite direction (+7%, -13%) in the ipsilateral frontal cortex. Qualitatively similar changes occurred in the ipsilateral parietal cortex. The CoBF measurements showed a marked vasodilation (131 and 108% in the frontal and parietal cortex, respectively) in parallel with the PO2 increase, followed by a prolonged (60 min), moderate hypoperfusion (maximum -17% at 20 min after CSD). There was a pronounced reduction of vascular reactivity to both hypercapnia (20.3% of the control response) and substantia innominata stimulation (1/6 of the response obtained 80 min later) at 10 min after CSD. Both reactivities progressively recovered in approximately 2 h. Since the issue of CSD in human has become a popular hypothesis for **migraine**, the reduced cerebrovascular reactivity could constitute the basis of a test for the involvement of CSD in **migraine**." [Abstract]

Yoon RS, Czaya A, Kwan HC, Joy ML.

Changes in the complex permittivity during spreading depression in rat cortex.

IEEE Trans Biomed Eng. 1999 Nov;46(11):1330-8.

"With recent developments in current density imaging (CDI), it is feasible to utilize this new technique in brain imaging applications. Since CDI's ability to measure changes in current

KCl application inhibited the **cortical** hypoperfusion that followed KCl application. c-Fos-like immunoreactivity, an indicator of neuronal activation, was detected in the ipsilateral, but not in the contralateral frontoparietal cortex 2 hr after KCl application. Lomerizine (3-30 mg/kg, p.o.) and flunarizine (30 mg/kg, p.o.) significantly attenuated the expression of c-Fos-like immunoreactivity in the ipsilateral frontoparietal cortex. Lomerizine was 3 to 1000 times more potent than flunarizine in the above SD models. These findings suggest that the inhibitory effects of lomerizine and flunarizine on the interval between the initiated and subsequent spontaneous SDs, the **cortical** hypoperfusion and expression of c-Fos-like immunoreactivity induced by SD are mediated via the effects of Ca2+ entry blockade, which may include an increase in cerebral blood flow and the prevention of excessive Ca2+ influx into brain cells." [Abstract]

Kaube H, Goadsby PJ.

Anti-migraine compounds fail to modulate the propagation of cortical spreading depression in the cat.

Eur Neurol. 1994;34(1):30-5.

"Leao's **cortical spreading** depression (SD) is often cited as the pathophysiological substrate for the neurological symptoms of **migraine** with aura. If this is the case it might be expected that drugs useful as anti-**migraine** agents, particularly those useful in prophylaxis, may alter or prevent SD. Indeep it has been suggested that the anti-**migraine** compound dihydroergotamine (DHE) blocks or reduces the speed of propagation of SD in the rabbit. In this study we attempted to further investigate the effects of DHE and other anti-**migraine** drugs on SD by measuring **cortical** blood flow with laser Doppler flowmetry (CBFLDF) and **cortical** single unit activity in the alpha-chloralose-anaesthetised cat. The following substances were tested: DHE, acetylsalicylic acid, lignocaine, metoprolol, clonazepam and valproate. The NMDA-receptor blocker MK-801 and halothane (1.5%) were used as reference substances that reliably block SD. The outcome measures were speed of propagation of the wave of SD across the cortex and the CBFLDF increase during the hyperaemic phase of SD. Data were taken from three control episodes (60 min apart) and after drug administration. The rate of propagation was significantly reduced from the first control period (3.0 +/- 0.3 mm/min) to the subsequent 2 control observations (2.3 +/- 0.1 mm/min) even without any drug treatment. Following the control observations the test drug was administered and a further SD elicited. This fourth SD was reliably blocked by MK-801 and halothane. None of the other test drugs inhibited SD, reduced the rate of propagation or changed the amplitude of the CBFLDF increase." [Abstract]

Fuentes B, Diez Tejedor E, Pascual J, Coya J, Quirce R.

Cerebral blood flow changes in pseudomigraine with pleocytosis analyzed by single photon emission computed tomography. A spreading depression mechanism?

Cephalalgia. 1998 Oct;18(8):570-3; discussion 531.

"Pseudomigraine with pleocytosis is a benign and autolimited syndrome. The etiology has been related to viral infection, but its pathophysiology is not yet well identified. To investigate this point, and to see if there were changes in cerebral blood flow (as in **migraine**), we performed single photon emission

density depends on a concomitant activity-dependent change in the conductivity of the brain tissue, we have examined the changes in complex conductivity during **spreading** depression (SD) in rodent neocortex using a coaxial probe. SD was chosen because it is often referred to as an animal model of cerebral ischemia and **migraine** with aura. The conductivity measurements revealed a change with short latency (30-60 s) followed by a change with a longer latency (200-300 s). This change in conductivity with short latency has not been reported before, and we conjecture that it may be the priming or triggering mechanism prior to the main SD episode. A 20% change in conductivity during SD is sufficiently large to be measured by CDI. Therefore, the ability to measure changes in the conductivity, as opposed to metabolic changes, makes CDI a viable approach to the study of ischemia and **migraine** with aura." [Abstract]

James MF, Smith MI, Bockhorst KH, Hall LD, Houston GC, Papadakis NG, Smith JM, Williams AJ, Xing D, Parsons AA, Huang CL, Carpenter TA.

Cortical spreading depression in the gyrencephalic feline brain studied by magnetic resonance imaging.

J Physiol. 1999 Sep 1;519 Pt 2:415-25.

"1.Time-lapse diffusion-weighted magnetic resonance imaging (DWI) was used to detect and characterize complex waves of **cortical spreading** depression (CSD) evoked with KCL placed upon the suprasylvian gyrus of anaesthetized cats. 2.The time-lapse representations successfully demonstrated primary CSD waves that propagated with elliptical wavefronts selectively over the ipsilateral cerebral hemispheres with a velocity of 3.8 +/- 0.70 mm min(-1) (mean +/- S.E.M. of 5 experiments). 3.In contrast, the succeeding secondary waves often remained within the originating gyrus, were slower (velocity 2.0 +/- 0.18 mm min(-1), more fragmented and varied in number. 4.Computed traces of the apparent diffusion coefficients (ADCs) showed negative deflections followed by monotonic decays (amplitudes: primary wave, -19.9 +/- 2.8%; subsequent waves, -13.6 +/- 1.9% duration at half-maximal decay, 150-200 s) when determined from regions of interest (ROIs) through which both primary and succeeding CSD waves propagated. 5.The passage of both the primary and the succeeding waves often correlated with transient DC potential deflections recorded from the suprasylvian gyrus. 6.The detailed waveforms of the ADC and the T2*-weighted (blood oxygenation level-dependent: BOLD) traces showed a clear reciprocal correlation. These imaging features that reflect disturbances in cellular water balance agree closely with BOLD measurements that followed the propagation velocities of the first and subsequent CSD events. They also provide a close physiological correlate for clinical observations of **cortical** blood flow disturbances associated with human **migraine**." [Abstract]

Wu YJ, Boissard CG, Greco C, Gribkoff VK, Harden DG, He H, L'Heureux A, Kang SH, Kinney GG, Knox RJ, Natale J, Newton AE, Lehtinen-Oboma S, Sinz MW, Sivarao DV, Starrett JE Jr, Sun LQ, Tertyshnikova S, Thompson MW, Weaver D, Wong HS, Zhang L, Dworetzky SI.

(S)-N-[1-(3-Morpholin-4-ylphenyl)ethyl]- 3-phenylacrylamide: An Orally Bioavailable KCNQ2 Opener with Significant Activity in a Cortical Spreading Depression Model of Migraine.

J Med Chem. 2003 Jul 17;46(15):3197-3200.

"S)-N-[1-(3-Morpholin-4-ylphenyl)ethyl]-3-phenylacrylamide (2)

computed tomography (SPECT) studies in four patients who fulfilled the diagnostic criteria for this syndrome. This was done during the acute phase and we repeated SPECT after resolution of the syndrome in two of them. We found a reduction in brain blood flow on the side of origin of the neurological deficits during the acute phase. This normalized after recovery of the syndrome. The finding suggests that the neurological deficits in this syndrome could be produced by a **spreading** depression-like mechanism similar to that proposed for **migraine** with aura." [Abstract]

Leniger T, Von Den Driesch S, Isbruch K, Diener HC, Hufnagel A.

Clinical characteristics of patients with comorbidity of migraine and epilepsy.

Headache. 2003 Jun;43(6):672-7.

"Objective.-Neuronal hyperexcitability might explain the comorbidity of **migraine** and epilepsy. **Spreading** depression, a postulated pathophysiological mechanism of epileptic seizures and **migraine** with aura, may hypothetically be the link between the disorders in these comorbid conditions. The aim of the present study was to determine whether certain clinical characteristics associated with **spreading** depression are overrepresented in patients with comorbidity. Methods.-In an outpatient clinic-based series, clinical characteristics of 61 patients with a comorbidity of **migraine** and epilepsy were compared to those of 280 patients with epilepsy alone and 248 patients with **migraine** alone. Patients were interviewed with a standardized questionnaire. Results.-The proportion of females was significantly higher in patients with comorbidity and patients with **migraine** as compared to patients with epilepsy (P <.001). Comparing patients with epilepsy and comorbidity, the frequency of epilepsy syndromes and seizure types was not significantly different. Comparing patients with **migraine** and comorbidity, **migraine** with aura was significantly more frequent in patients with comorbidity (P =.019). Other **migraine** features such as moderate to severe pain intensity, worsening of pain on activity, phonophobia, and photophobia were significantly more frequent in patients with comorbidity as compared to patients with **migraine** (P </=.001). Conclusion.-No specific epileptic characteristics could be found in patients with comorbidity. Altered cerebral excitability resulting in an increased occurrence of **spreading** depression may explain the differences in **migraine** attacks in patients with comorbidity as compared to patients with **migraine** alone." [Abstract]

Kaube H, Limmroth V.

[Animal models and their results in relation to the therapy of migraine]

Schmerz. 1996 Jun 17;10(3):114-20.

"Until now, our understanding of **migraine** pathophysiology has been fairly incomplete. So far no animal model has allowed an explanation of all facets of the clinically heterogenous condition **migraine**. However, it is now generally accepted that the **migraine** headache is due to activation of the trigeminal system. The model of neurogenic inflammation after stimulation of the trigeminal ganglion or systemic administration of capsaicin allows study of the inhibitory interactions between antimigraine compounds and peripheral trigeminal fibre terminals that sustain a sterile meningeal inflammation through release of alogenic and vasoactive neuropeptides, such as substance P and calcitonin gene-related peptide. Studies with the model of superior

was synthesized as an orally bioavailable KCNQ2 potassium channel opener. In a rat model of **migraine**, 2 demonstrated significant oral activity in reducing the total number of **cortical spreading** depressions induced by potassium chloride." [Abstract]

Gorji A, Scheller D, Tegtmeier F, Kohling R, Straub H, Speckmann EJ.

NiCl2 and amiloride induce spreading depression in guinea pig hippocampal slices.

Cephalalgia. 2000 Oct;20(8):740-7.

"**Spreading** depressions (SD) occur in association with ischaemia, epilepsy and **migraine**. Intracellular calcium oscillations have been suggested to be involved in the generation and propagation of SD. The present study was performed to study the mechanism of conditioning guinea pig hippocampal slices by the T-type calcium channel blockers NiCl2 and amiloride. SD-like fluctuations of DC potential were recorded by inserting microelectrodes into the CA1 and CA3 regions. The SD occurrence was significantly greater with 10 micromol/l NiCl2 as well as with 25 and 50 micromol/l amiloride than with other concentrations of these substances. The concentration response curve was inversely U-shaped with the maximum repetition rates of SDs being achieved at 10 micromol/l NiCl2 as well as at 25 and 50 micromol/l amiloride. SD occurrence could be completely blocked by the NMDA antagonist APV (10 micromol/l) in all cases. These data demonstrate that modulation of the Ca2+ dynamics conditioned guinea pig hippocampal slices and increased their susceptibility to generate SD." [Abstract]

Peters O, Schipke CG, Hashimoto Y, Kettenmann H.

Different mechanisms promote astrocyte Ca2+ waves and spreading depression in the mouse neocortex.

J Neurosci. 2003 Oct 29;23(30):9888-96.

"**Cortical spreading** depression (CSD) is thought to play an important role in different pathological conditions of the human brain. Here we investigated the interaction between CSD and Ca2+ waves within the astrocyte population in slices from mouse neocortex (postnatal days 10-14). After local KCl ejection as a trigger for CSD, we recorded the propagation of Ca2+ increases within a large population of identified astrocytes in synchrony with CSD measured as intrinsic optical signal (IOS) or negative DC-potential shift. The two events spread with 39.2 +/- 3.3 mum/sec until the IOS and negative DC-potential shift decayed after approximately 1 mm. However, the astrocyte Ca2+ wave continued to propagate for up to another 500 microm but with a reduced speed of 18.3 +/- 2.5 microm/sec that is also typical for glial Ca2+ waves in white matter or culture. While blocking CSD using MK-801 (40 microm), an NMDA-receptor antagonist, the astrocyte Ca2+ wave persisted with a reduced speed (13.2 +/- 1.5 microm/sec). The specific gap junction blocker carbenoxolon (100 microm) did not prevent CSD but decelerated the speed (2.9 +/- 0.9 microm/sec) of the astrocyte Ca2+ wave in the periphery of CSD. We also found that interfering with intracellular astrocytic Ca2+ signaling by depletion of internal Ca2+ stores does not affect the spread of the IOS. We conclude that CSD determines the velocity of an accompanying astrocytic Ca2+ response, but the astrocyte Ca2+ wave penetrates a larger territory and by this represents a self-reliant phenomenon with a different mechanism of propagation." [Abstract]

Dienel GA, Liu K, Cruz NF.

Local uptake of (14)C-labeled acetate and butyrate

sagittal sinus stimulation have revealed central actions of antimigraine agents such as ergotamine and sumatriptan, but also acetylsalicylic acid on neurotransmission of trigeminal nociceptive input in the brainstem. A likely explanation for the slowly progressing neurological deficits is **cortical spreading** depression (CSD), which can easily be elicited in many species. However, CSD has not been observed in vivo in humans. The described models strongly influenced the development of new medications for **migraine** treatment and have improved our understanding of **migraine** pathophysiology." [Abstract]

Piper RD, Lambert GA.

Inhalational anesthetics inhibit spreading depression: relevance to migraine.

Cephalalgia. 1996 Apr;16(2):87-92.

"**Cortical spreading** depression (SD) has not been shown in the human neocortex by direct **cortical** recordings. However, animal studies suggest that **cortical** injury, such as that occurring during neurosurgical procedures, should result in the initiation of SD. It is possible that inhibition of SD by volatile anesthetic agents may partially explain the failure to observe SD in the human neocortex during surgery. This study examines the effect of the anesthetic agents alpha-chloralose, halothane, nitrous oxide and isoflurane on the initiation of **cortical** SD in the cat neocortex. SD was seen in 100% of cats anesthetized with alpha-chloralose ($n = 15$), in 3 of 7 (42%) animals anesthetized with isoflurane ($p < 0.05$, chi 2 with Yates correction) and none of the animals ($n = 4$, 6 hemispheric preparations) anesthetized with halothane ($p < 0.005$, chi 2 with Yates correction, halothane vs alpha-chloralose group). In all cases this inhibitory effect was reversible. In four animals the administration of nitrous oxide (66%) reduced the inspired concentration of isoflurane required to inhibit SD by 0.75%. This study suggests that halothane, and to a lesser extent isoflurane and nitrous oxide, protect against the initiation of **cortical** SD. This observation may partially explain why SD has not been demonstrated in human neocortex during surgery. Further studies are needed to determine if SD may occur under pathological conditions, such as during **migraine** with aura, where the cortex may be predisposed to SD." [Abstract]

Kunkler PE, Kraig RP.

Hippocampal spreading depression bilaterally activates the caudal trigeminal nucleus in rodents.

Hippocampus. 2003;13(7):835-44. [Abstract]

Koroleva VI, Bures J.

Rats do not experience cortical or hippocampal spreading depression as aversive.

Neurosci Lett. 1993 Jan 12;149(2):153-6.

"**Cortical spreading** depression (SD) may produce some symptoms of the aura of classical **migraine** but it is less probable that it can account for the headache. The aversiveness of SD was examined in unanesthetized rats. In Exp. 1, rats with implanted **cortical** cannulae were confined in the dark compartment of the step-through apparatus and repeated waves of SD were elicited in one hemisphere. After two such training sessions the rats did not evince passive avoidance of the compartment associated with **cortical** SD. In

in rat brain in vivo during spreading cortical depression.

J Neurosci Res. 2001 Dec 1;66(5):812-20.

"**Spreading** depression severely disrupts ion homeostasis, causes sensory neglect and motor impairment, and is associated with stroke and **migraine**. Glucose utilization (CMR(glc)) and lactate production rise during **spreading** depression, but the metabolic changes in different brain cell types are unknown. Uptake of (14) C-labeled compounds known to be preferentially metabolized by the glial tricarboxylic acid cycle was, therefore, examined during unilateral KCl-induced **spreading cortical** depression in conscious, normoxic rats. [(14)C]Metabolites derived from [(14) C]butyrate in K+ -treated tissue rose 21% compared to that of untreated contralateral control cortex, whereas incorporation of H (14)CO(3) into metabolites in K+ -treated tissue was reduced to 86% of control. Autoradiographic analysis showed that laminar labeling of cerebral cortex by both (14)C-labeled acetate and butyrate was elevated heterogeneously throughout cortex by an average of 23%; the increase was greatest (approximately 40%) in tissue adjacent to the K+ application site. Local uptake of acetate, butyrate, and deoxyglucose showed similar patterns, and monocarboxylic acid uptake was highest in the structures in which apparent loss of labeled metabolites of [6-(14)C]glucose was greatest. Enhancement of net uptake of acetate and butyrate in cerebral cortex during **spreading** depression is tentatively ascribed to increased astrocyte metabolism." [Abstract]

Ruppin E, Reggia JA.

Cortical spreading depression and the pathogenesis of brain disorders: a computational and neural network-based investigation.

Neurol Res. 2001 Jul;23(5):447-56.

"This paper reviews our recent studies of the role of **cortical spreading** depression (CSD) in the pathogenesis of brain disorders. Our investigation is a computational one, involving the development and utilization of a complex neuro-metabolic model of the interactions assumed to occur in the cortex during the passage of multiple CSD waves. Incorporating these neuro-metabolic changes of CSD within a neural network model of normoxic cortex produces **cortical** activation patterns during the passage of a CSD wave that, projected onto the visual fields, resemble the visual hallucinations observed during the **migraine** aura. When focal ischemia is simulated with the model, the evoked CSD waves are found to affect the expansion of the infarction into the ischemic penumbra. Our findings support the hypothesis that CSD does play an important pathogenic role in these and other neurological disorders, and suggest additional experimental studies that may further substantiate it." [Abstract]

Ebersberger A, Schaible HG, Averbeck B, Richter F.

Is there a correlation between spreading depression, neurogenic inflammation, and nociception that might cause migraine headache?

Ann Neurol. 2001 Jan;49(1):7-13.

"The time course of propagation of scotoma and blood flow changes during **migraine** aura parallels the phenomenon of **cortical spreading** depression (CSD). It was proposed that CSD generates a sterile neurogenic inflammation in the meninges, which may then lead to the activation or sensitization of nociceptors, thus generating headache. We performed rat experiments in which the effect of CSD on plasma extravasation in the dura mater and on neuronal activity in deep laminae of the trigeminal nucleus was assessed in vivo. CSD did not alter dural

Exp. 2, thirsty rats with implanted hippocampal electrodes were trained to drink from two different spouts A and B. Hippocampal SD was elicited when the animal was drinking from spout A but not from spout B. Drinking was interrupted shortly after appearance of the SD wave and gradually recovered over the subsequent 10 min, but up to ten spout A-SD pairings did not change the animal's preference for spout A. It is concluded that **cortical** or hippocampal SD has no immediate or delayed aversive consequences." [Abstract]

plasma extravasation measured by means of bovine serum albumin-coupled flourescein (n = 17 rats) compared to the CSD-free contralateral side. In an in vitro model, the application of KCl to the dura at concentrations extracellularly found during CSD did not alter the release of calcitonin gene-related peptide and prostaglandin E2 from the dura. In 33 rats, neither single CSDs nor a series of CSDs altered ongoing neuronal activity or mechanical and/or thermal sensitivity of the deeply located neurons to stimulation of their receptive fields in the dura mater. These results are at variance with data that showed increased c-Fos labeling in superficial laminae of the trigeminal nucleus following CSD. They do not suggest that CSD initiates **migraine** headache via neurogenic inflammation." [Abstract]

Dreier JP, Kleeberg J, Petzold G, Priller J, Windmuller O, Orzechowski HD, Lindauer U, Heinemann U, Einhaupl KM, Dirnagl U.

Endothelin-1 potently induces Leao's cortical spreading depression in vivo in the rat: a model for an endothelial trigger of migrainous aura?

Brain. 2002 Jan;125(Pt 1):102-12.

"According to the 'neuronal' theory, **cortical spreading** depression (CSD) is the pathophysiological correlate of migrainous aura. However, the 'vascular' theory has implicated altered vascular function in the induction of aura symptoms. The possibility of a vascular origin of aura symptoms is supported, e.g. by the clinical observation that cerebral angiography frequently provokes migrainous aura. This suggests that endothelial irritation may somehow initiate one of the pathways resulting in migrainous aura. Up to now, an endothelium-derived factor has never been shown to trigger CSD. Here, for the first time, we demonstrate and characterize the ability of the vasoconstrictor and astroglial/neuronal modulator endothelin-1 to trigger Leao's '**spreading** depression of activity' in vivo in rats. At a concentration range between 10 nM and 1 microM, endothelin-1 induced changes characteristic of CSD with regard to the rate of propagation, steady (direct current) potential and extracellular K(+)-concentration. A **spreading** hyperaemia followed by oligaemia was observed similar to those in K(+)-induced CSD. Endothelin-1 did not provoke changes characteristic of a terminal depolarization. The mechanism by which endothelin-1 generated CSD involved the N-methyl-D-asparate receptor. Cerebral blood flow decreased slightly, but significantly, before endothelin-1 generated CSD. A vasodilator (NO*-donor) shifted the threshold for CSD induction to higher concentrations of endothelin-1. Endothelin-1, in contrast to K(+), did not induce CSD in rat brain slices suggesting indirectly that endothelin-1 may require intact perfusion to exert its effects. In conclusion, endothelin-1 was found in the experiment to be the most potent inducer of CSD currently known. We propose endothelin-1 as a possible candidate for the yet enigmatic link between endothelial irritation and migrainous aura." [Abstract]

Goadsby PJ, Adner M, Edvinsson L.

Characterization of endothelin receptors in the cerebral vasculature and their lack of effect on spreading depression.

J Cereb Blood Flow Metab. 1996 Jul;16(4):698-704.

"The changes in cerebral blood flow that accompany **spreading** depression are well-described, as are parallel changes in cellular activity, with a wave of hyperemia followed by a prolonged oligemic phase. In this study, a cat model of the CBF changes associated with **spreading** depression and in vitro pharmacology were used to determine if there is a role for the powerful peptide

vasoconstrictor endothelin in this response. For the pharmacological studies, the middle cerebral artery was harvested from cats postmortem. For the physiological studies, cats were anesthetized with halothane induction and alpha-chloralose (60 mg/kg, intraperitoneal loading; 20 mg/kg i.v. 2-h maintenance). CBF was monitored continuously in the parietal cortex using laser Doppler flowmetry (CBFLDF) after exposure of the dura mater. The in vitro work demonstrated that endothelin-1 (ET-1) mediates a strong and potent contraction of cerebral vessels. Both the selective ETA receptor antagonist FR139317 and the combined ETA and ETB receptor antagonist Bosentan caused a rightward shift of the concentration-response curve without attenuation of the maximum effect. The calculated pA2 values were 6.28 and 6.90, respectively. The slope did not differ from unity, suggesting that the ET-1-mediated contraction is evoked by a single population of ETA receptors, which were effectively antagonized by these compounds. **Spreading** depression was induced with a needle stick injury to the cortex. Local administration of the endothelin antagonists FR139317 (10 microM) and Bosentan (10 microM) did not affect resting blood flow in the cortex. Induction of **spreading** depression following local administration of FR139317 and Bosentan resulted in responses no different from those in control cortex. These data demonstrate that endothelin does not play a significant role in the vasoconstrictor portion of the CBF change seen in **spreading** depression, nor does it affect resting flow. Since it is widely held that **spreading** depression, or a very similar mechanism, underlies the aura phase of **migraine**, it may be suggested from these studies that endothelin antagonists are unlikely to be useful in **migraine**." [Abstract]

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Recent **Migraine** and **Cortical Spreading** Depression Research

Sanchez-Del-Rio M, Reuter U, Moskowitz MA

New insights into migraine pathophysiology.

Curr Opin Neurol. 2006 Jun;19(3):294-298.

PURPOSE OF REVIEW: This article will review new and exciting developments in **migraine** research, with particular emphasis on mutations associated with familial hemiplegic **migraine** and the role of **cortical spreading** depression in its pathophysiology and treatment. RECENT FINDINGS: The recent discovery of multiple point mutations in familial hemiplegic **migraine** has led to the suggestion that **migraine** and its variants may be due to a paroxysmal disturbance in ion-translocating mechanisms. Mutations associated with familial hemiplegic **migraine** render the brain more susceptible to prolonged **cortical spreading** depression caused by either excessive synaptic glutamate release or decreased removal of glutamate and potassium from the synaptic cleft, or persistent sodium influx. Suppression of **cortical spreading** depression has become an interesting target for preventive **migraine** treatment. Prolonged treatment with beta-blockers, valproate, topiramate, methysergide or amitriptyline reduced the number of potassium-evoked **cortical spreading** depressions and elevated the electrical stimulation threshold for the induction of **cortical spreading** depression in rats. Recent imaging studies in patients suffering from **migraine** without aura also point to the presence of silent **cortical spreading** depression as an underlying mechanism. Repeated waves of **cortical spreading** depression may have deleterious effects on brain function, and perhaps cause silent ischaemic lesions in vulnerable brain regions such as the cerebellum in susceptible individuals. SUMMARY: This review emphasizes several neurobiological aspects of **migraine** that reveal paroxysmal disturbances in neuronal and vascular function, that in turn reflect disturbances in the maintenance of ionic gradients. [Abstract]

Agostoni E, Aliprandi A

The complications of migraine with aura.

Neurol Sci. 2006 May;27 Suppl 2S91-5.

Migraine with aura is a common disorder in industrialised countries, affecting up to 5% of the adult population. Although **migraine** aura is usually a benign disorder, in rare instances it can be the cause of serious neurologic complications. The most common is migrainous stroke, defined as a persistent neurologic deficit following the aura with evidence of brain infarction at neuroimaging and lack of alternative explanations. The most likely pathogenic mechanism is brain ischaemia induced by **cortical spreading** depression, but other possibilities, such as intracranic arterial dissection or embolism through patent foramen ovale need to be considered. Other complications are **migraine**-related seizures, which are probably caused by neuronal hyperexcitability in migraineurs, and persistent auras without infarction. These disorders are

of both clinical and scientific interest, as they throw light on the complex and not yet fully understood relationship between **migraine** with aura, stroke and epilepsy. [Abstract]

Dalkara T, Zervas NT, Moskowitz MA

From spreading depression to the trigeminovascular system.

Neurol Sci. 2006 May;27 Suppl 2S86-90.

Migraine headaches have a complex pathophysiology; both vascular and neuronal mechanisms have been proposed. One possible scenario begins with brain-initiated events evolving to **cortical spreading** depression (CSD), which in turn activates the trigeminal nerve to cause headaches. Experimental evidence supports a relationship between CSD as a cause of **migraine** aura as well as CSD as a cause of trigeminal activation. Susceptibility to CSD and to **migraine** appears to be genetically determined. In some **migraine** subtypes, genes controlling translocation of calcium, sodium and potassium have been implicated, perhaps altering the susceptibility to CSD. This chapter briefly reviews current knowledge pertaining to **migraine** pathophysiology with emphasis on current notions linking disturbances in ion flux to the genesis of headache. [Abstract]

Pierangeli G, Cevoli S, Sancisi E, Grimaldi D, Zanigni S, Montagna P, Cortelli P

Which therapy for which patient?

Neurol Sci. 2006 May;27 Suppl 2S153-8.

Prophylactic treatment is mainly intended to reduce the frequency of **migraine** attacks, enhance response to acute medications, improve patient function and reduce disability. Sufficient evidence and consensus exist to recommend propranolol, timolol, amitriptyline, pizotifen, divalproex, sodium valproate and topiramate as first line agents for **migraine** prevention. These drugs can halve the frequency of attacks in 50% of patients. The anticipated benefit must be weighed against the adverse effects associated with each agent in determining the optimal preventive regimen for individual patients considering any comorbid conditions that are often present. The decision to treat and the choice of prophylactic drug must be taken with the patient. It is important to balance expectations and therapeutic realities for each particular drug. Recent data on the effect of prophylactic treatment on trigeminovascular activation and on **cortical spreading** depression emphasise the importance of developing research on **migraine**-preventive drugs. [Abstract]

Longoni M, Ferrarese C

Inflammation and excitotoxicity: role in migraine pathogenesis.

Neurol Sci. 2006 May;27 Suppl 2S107-10.

The pathogenesis of **migraine** is still unclear, but much evidence suggests a role of inflammation in pain generation. Calcitonin gene related peptide, nitric oxide and cytokines are all molecules shown to be involved both in animal and human studies. The glutamatergic system is also described as a possible mechanism leading to neuronal hyperexcitability and **cortical spreading** depression (CSD). Excitotoxic neural death, due to excessive release of the amino acid in the extracellular space, may represent a consequence of protracted CSD and oligaemia and may be involved in migrainous infarction and aspecific lesions seen on T2-weighted NMR imaging. [Abstract]

Liebetanz D, Fregni F, Monte-Silva KK, Oliveira MB, Ambncio-dos-Santos A, Nitsche MA, Guedes RC

After-effects of transcranial direct current stimulation (tDCS) on cortical spreading depression.

Neurosci Lett. 2006 May 1;398(1-2):85-90.

Abnormal **cortical** excitability influences susceptibility to **cortical spreading** depression (CSD) in **migraine**. Because transcranial direct current stimulation (tDCS) is capable of inducing lasting changes of **cortical** excitability, we investigated the after-effects of tDCS on the propagation velocity of CSD in the rat. Twenty-five anesthetised rats received either anodal, cathodal or sham tDCS. The stimulation was applied for 20 min at a current strength of 200 microA after the recording of three baseline CSD measurements. Starting 5 min after tDCS, a further three CSDs were elicited and CSD velocity recorded at intervals of 20 min. tDCS and CSD recording was performed under anaesthesia with chloralose and urethane. As compared to the baseline velocity of 3.14 mm/min, anodal tDCS induced a significant increase of propagation velocity during the first post-tDCS recording (3.49 mm/min). In contrast to anodal tDCS, neither cathodal tDCS nor sham tDCS, which consisted of an initial ramped DC stimulation lasting only 20 s, showed a significant effect on CSD propagation velocity. As anodal tDCS is known to induce a lasting increase of **cortical** excitability in the clinical setting, our results support the notion that CSD propagation velocity reflects **cortical** excitability. Since **cortical** excitability and susceptibility to CSD is elevated in **migraine** patients, anodal tDCS - by increasing **cortical** excitability - might increase the probability of **migraine** attack in these patients, even beyond the end of its application. [Abstract]

Ayata C, Jin H, Kudo C, Dalkara T, Moskowitz MA

Suppression of cortical spreading depression in migraine prophylaxis.

Ann Neurol. 2006 Apr;59(4):652-61.

OBJECTIVE: Topiramate, valproate, propranolol, amitriptyline, and methysergide have been widely prescribed for **migraine** prophylaxis, but their mechanism or site of action is uncertain. **Cortical spreading** depression (CSD) has been implicated in **migraine** and as a headache trigger and can be evoked in experimental animals by electrical or chemical stimulation. We hypothesized that **migraine** prophylactic agents suppress CSD as a common mechanism of action. METHODS: Rats were treated either acutely or chronically over weeks and months, with one of the above **migraine** prophylactic drugs, vehicle, or D-propranolol, a clinically ineffective drug. The impact of treatment was determined on the frequency of evoked CSDs after topical potassium application or on the incremental cathodal stimulation threshold to evoke CSD. RESULTS: Chronic daily administration of **migraine** prophylactic drugs dose-dependently suppressed CSD frequency by 40 to 80% and increased the cathodal stimulation threshold, whereas acute treatment was ineffective. Longer treatment durations produced stronger CSD suppression. Chronic D-propranolol treatment did not differ from saline control. INTERPRETATION: Our data suggest that CSD provides a common therapeutic target for widely prescribed **migraine** prophylactic drugs. Assessing CSD threshold may prove useful for developing new

prophylactic drugs and improving upon existing ones. [Abstract]

Gupta V

Anisometropia and migraine: is the link to cortical spreading depression logically defensible?

J Neurol. 2006 Mar 6; [Abstract]

Ramadan NM

Migraine headache prophylaxis: current options and advances on the horizon.

Curr Neurol Neurosci Rep. 2006 Mar;6(2):95-9.

Migraine is increasingly recognized as a disorder of altered neuronal excitability, in part based on genetically mediated and environmentally modified aberrations of ionic exchange across the brain neuronal membrane. To this end, **migraine** pharmacotherapy aids in restoring the abnormally low threshold for neuronal excitation. Indeed, modulation of neuronal excitability is a common property of several established **migraine** preventive drugs such as propranolol, valproate, amitriptyline, and topiramate. Future **migraine** preventive pharmacologic therapies likely will aim at restoring the neuronal threshold for excitation by targeting such processes as **cortical spreading** depression and intracellular calcium influx. Also, strategies aimed at enhancing descending antinociceptive inhibition will yield effective antimigraine drugs. [Abstract]

Wernsmann B, Pape HC, Speckmann EJ, Gorji A

Effect of cortical spreading depression on synaptic transmission of rat hippocampal tissues.

Eur J Neurosci. 2006 Mar;23(5):1103-10.

Cortical spreading depression (CSD) is believed to be a putative neuronal mechanism underlying **migraine** aura and subsequent pain. In vitro and ex vivo/in vitro brain slice techniques were used to investigate CSD effects on the field excitatory postsynaptic potentials (fEPSP) and tetanus-induced long-term potentiation (LTP) in combined rat hippocampus-cortex slices. Induction of CSD in combined hippocampus-cortex slices in which DC negative deflections did not propagate from neocortex to hippocampus significantly augmented fEPSP amplitude and LTP in the hippocampus. Propagation of CSD to the hippocampus resulted in a transient suppression followed by reinstatement of fEPSP with amplitude of pre-CSD levels. LTP was inhibited when DC potential shifts were recorded in the hippocampus. Furthermore, CSD was induced in anaesthetized rats and, thereafter, hippocampal tissues were examined in vitro. LTP was significantly enhanced in hippocampal slices obtained from ipsilateral site to the hemisphere in which CSD was evoked. The results indicate the disturbances of hippocampal synaptic transmission triggered by propagation of CSD. This perturbation of hippocampal synaptic transmission induced by CSD may relate to some symptoms occurring during **migraine** attacks, such as amnesia and hyperactivity. [Abstract]

Sellal F

[Transient amnesia in the elderly]

Psychol Neuropsychiatr Vieil. 2006 Mar;4(1):31-8.

The two main aetiologies of transient amnesia in the elderly are idiopathic transient global amnesia (TGA) and iatrogenic or toxic amnesia. Vascular and epileptic amnesia are less common. According to the literature, transient psychogenic amnesia, which is a frequent cause of amnesia at age 30 to 50, is very rare in the elderly. TGA is the prototypical picture of transient amnesia. It occurs more often after age 50, with no identified cause, even if some authors accept emotional stress or minor head trauma as occasional precipitants. The mechanism of TGA remains a matter of discussion. It may be the consequence of a **spreading** depression similar to that described in **migraine** with aura, but other arguments support an ischemic mechanism. Iatrogenic amnesias are mainly caused by benzodiazepines (BZs) or anticholinergics. The former may occur in a non-anxious subject, who is not a usual consumer of BZ and takes a single dose. The latter are more often due to a hypersensitivity to anticholinergic drugs, in particular in patients presenting with a covert, incipient Alzheimer's disease. A vascular origin must be considered when amnesia is accompanied by other neurological symptoms, and when the regression of the amnesic disorder is slow, lasting several days. It results from lesions involving various mechanisms and locations, mainly subcortical. Partial seizures, most often mesio-temporal, more rarely frontal, may be the cause of transient amnesia in the elderly, in the absence of a past history of epilepsy. The red flag supportive of an epileptic origin is the repetition of stereotyped amnesic episodes. EEG demonstration of seizures may be difficult and the response to antiepileptic drugs effective on partial seizures is usually good. [Abstract]

Gremillion HA, Stover MR

Cortical spreading depression of migraine: overview and clinical implications.

Tex Dent J. 2006 Feb;123(2):154-63. [Abstract]

Supornsilpchai W, Sanguanrangsirikul S, Maneesri S, Srikiatkhachorn A

Serotonin depletion, cortical spreading depression, and trigeminal nociception.

Headache. 2006 Jan;46(1):34-9.

BACKGROUND: The attack of **migraine** has been observed to be associated with low level of serotonin (5-HT). Although the mechanism underlying this relationship is still unclear, change in **cortical** excitability or susceptibility of trigeminal system is a possible explanation. Objectives: The aim was to study the effect of 5-HT depletion on the development of **cortical spreading** depression (CSD) and CSD-evoked trigeminal nociception. METHODS: Wistar rats were separated into low 5-HT and control groups (eight rats each). 5-HT was depleted by administration of para-chlorophenylalanine, a tryptophan hydroxylase inhibitor. CSD was induced by applying 3 mg of potassium chloride on parietal cortex. **Cortical** activity was monitored for 1 hour. Trigeminal nociception was determined using number of Fos-immunoreactive (Fos-IR) neurons in trigeminal nucleus caudalis as the indicator. RESULTS: Application of KCl led to the development of series of depolarization shift characteristics for CSD. The development of these CSD waves was enhanced in low 5-HT state. The area under curve of each CSD wave and the number of CSD waves occurring within 1 hour were greater in low 5-HT group. No significant change in peak amplitude and duration

of CSD wave was observed. The numbers of Fos-IR cells on ipsilateral and contralateral trigeminal nucleus caudalis were significantly greater in the low 5-HT group than those of the controls. CONCLUSION: Our findings indicate that 5-HT depletion enhances CSD-induced trigeminal nociception by increasing the **cortical** excitability and sensitivity of trigeminal nociceptive system. These findings may provide a better understanding regarding the relationship between low 5-HT and clinical headaches. [Abstract]

Gupta VK

Migrainous scintillating scotoma and headache is ocular in origin: A new hypothesis.

Med Hypotheses. 2006;66(3):454-60.

Brain neuronal dysfunction has been implicated in pathogenesis of **migraine** but direct evidence is lacking. Scintillating scotoma of **migraine** is generally believed to originate at the visual cortex. While **cortical spreading** depression is a relatively late physiological alteration in **migraine**, its protective role in neuronal ischaemia is increasingly being recognized. Atenolol, nadolol, or verapamil prevent **migraine** but do not readily cross the blood-brain barrier or critically influence any brain or peripheral neuronal function. Typical **migraine** headache, aura, or scintillating scotoma has not been reported following enucleation or evisceration of the eye. In humans, pain and temperature fibres from only the ophthalmic division of the trigeminal nerve reach the upper cervical spinal segments. Pain in **migraine** attacks including occipital and nuchal discomfort reflects selective involvement of the ophthalmic nerve. Photophobia is largely a retinal reflex involving the ophthalmic division of the trigeminal nerve. Key clinical features of the migrainous scintillating scotoma are consistent with retinal origin. **Spreading** depression in the retina is well-established. A subtle regional ocular sympathetic deficit prevails in **migraine** patients and possibly impairs regulation of intraocular choroidal blood volume and intraocular pressure. Several first-line **migraine** prophylactic agents lower the intraocular pressure. The neuro-ophthalmological basis for a monocular origin of migrainous scintillating scotomata due to mechanical deformation of the posterior segment of the corneo-scleral envelope consequent to choroidal venous congestion and rise in intraocular pressure is presented. Study of distribution and displaceability of the migrainous scintillating scotoma can settle its site of origin. Headache of **migraine** possibly arises from a similar mechanical deformation of the anterior eye segment followed by antidromic discharge in the trigeminovascular system. Lateralizing negative deficits such as homonymous hemianopia probably reflect vasospastic complications of **migraine**. A rational explanation for the most characteristic clinical features of **migraine** and a new template to elucidate the pharmacological basis of anti-**migraine** drugs is offered. [Abstract]

Lampl C, Katsarava Z, Diener HC, Limmroth V

Lamotrigine reduces migraine aura and migraine attacks in patients with migraine with aura.

J Neurol Neurosurg Psychiatry. 2005 Dec;76(12):1730-2.

This study examined the efficacy of lamotrigine in the prevention of **migraine** aura. Fifty nine patients suffering from **migraine** with aura received lamotrigine in a controlled three year prospective open study. Treatment response was defined as a reduction of aura frequency each month by at least 50%. Primary endpoint was reached by three quarters of the patients. Lamotrigine significantly reduced both frequency of **migraine** aura (mean, 1.5 (SD, 0.6) each month before v 0.4 (0.7) after treatment; $p < 0.001$) and aura duration (mean, 27 (SD, 11) minutes before v 8 (14) after treatment; $p < 0.001$). Furthermore, more than three quarters of those patients with a reduction of aura symptoms experienced a significant reduction of frequency of **migraine** attacks (mean, 2.1 (SD, 1.0) each month before v 1.2 (1.1) after treatment; $p < 0.001$). Lamotrigine was highly effective in reducing **migraine** aura and **migraine** attacks. The strong correlation between reduction of aura symptoms and **migraine** attacks stresses the potential role of aura-like events and possibly **cortical spreading** depression as a trigger for trigeminal vascular activation, and subsequently the development of **migraine** headaches. [Abstract]

Teive HA, Kowacs PA, Maranhco Filho P, Piovesan EJ, Werneck LC

Leao's cortical spreading depression: from experimental "artifact" to physiological principle.

Neurology. 2005 Nov 8;65(9):1455-9.

Cortical spreading depression was described in 1943 by Aristides Leco, a Brazilian neurophysiologist. Initially considered to be a mysterious event as it was discovered serendipitously, its nature has become progressively better known. **Cortical spreading** depression is now accepted as the mechanism underlying **migraine** aura and has became known as either Leco's **spreading** depression or **cortical spreading** depression. Recent studies have suggested a role for Leco's **cortical spreading** depression in the pathogenesis and symptomatology of neurologic disorders such as transient global amnesia, head injury, and cerebrovascular diseases. [Abstract]

Yavich L, Ylinen A

Spreading depression in the cortex differently modulates dopamine release in rat mesolimbic and nigrostriatal terminal fields.

Exp Neurol. 2005 Nov;196(1):47-53.

The effects of **cortical spreading** depression (SD) on evoked dopamine release in mesolimbic (nucleus accumbens) and nigrostriatal (nucleus caudatus) terminal fields were studied by in vivo voltammetry in anesthetized rats. Dopamine release was evoked by electrical stimulation of medial forebrain bundle (20 Hz, 100 pulses). Local application of 3 M KCl on the dura initiated SD in the cortex. It was found that SD modulated evoked dopamine release in subcortical structures at the same time when the wave of depression of **cortical** activity reached reciprocally connected subcortical areas. This **cortical** depression increased stimulated dopamine release in the nucleus accumbens and decreased dopamine release in the nucleus caudatus. In agreement with these results, electrical stimulation of the prefrontal cortex at 20 Hz, synchronized with medial forebrain bundle stimulation, decreased evoked dopamine release in the nucleus accumbens. Areas of the cortex which modulated dopamine release in these two terminal fields were spatially separated by at least 5 mm from each other. It is proposed that depression and activation of evoked dopamine release in the nucleus caudatus and nucleus accumbens following SD are indicative of tonic activation of the nigrostriatal and tonic inhibition of the mesolimbic dopaminergic terminals by cortex in normal conditions. SD in the cortex, modulating neurotransmitter release in subcortical structures, may have a general impact on redistribution of oxygen supply in these subcortical areas and on behavior associated with brain trauma, **migraine**, insult or seizures, i.e. the kind of neuropathology which may cause SD type

phenomena also in human brain. [Abstract]

Suzuki N

[Migraine-update--current concepts of migraine pathogenesis]

Rinsho Shinkeigaku. 2005 Nov;45(11):834-6.

The pathophysiology of **migraine** still remains unclear. However, abundant evidence in support of the view that **migraine** as an illness of the central nervous system has been accumulated. First, the hyperexitability in the brain is recognized even in the stage between attacks in migraineurs according to findings of transcranial magnetic stimulation techniques, MRI-BOLD studies or 31P SPECT examinations. Second, **cortical spreading** depression originating in the occipital cortex is more likely to be related to the aura. Third, sensitization of the trigeminal nerve system is substantially involved in process of headache pain in **migraine**. Fourth, clonic dysfunction of the priaqueductal gray matter in the brain stem may underlie the **migraine** pathogenesis. Thus, current concept of susceptibility of **migraine** is attributed to certain dysfunction of the deep brain structures such as the brain stem rather than the blood vessels in the brain or dura mater. [Abstract]

Kowa H, Takeshima T, Nakashima K

[Migraine update]

Nippon Rinsho. 2005 Oct;63(10):1733-41.

Migraine is one of the common diseases suffering 8.4 million patients in Japan. The pathophysiology of **migraine** remains unclear. The genetic and basic studies of the familial hemiplegic **migraine**, a specific subtype of **migraine** with aura, have demonstrated the dysfunction of mutant brain-expressed calcium ion channel and/or the Na+/K+ ion transporter and suggested the association between **cortical spreading** depression (CSD) and **migraine** with aura. It is suggested that the CSD, neurogenic inflammation and vasodilatation caused by unknown triggers may activate the 'brainstem **migraine** generator' and amplified back way. In consequence, headache and/or aura will be appeared and strengthened. Our etiological data of headache in Daisen located in Western Japan clarified as follows; 1) Overall prevalence of **migraine** in Daisen was 6.0%. Women observed a 5.9-fold higher risk of **migraine** than men. 2) Fatigue, mental stress, and lack of sleep were the main headache triggers. 3) Only 7.3% of those with **migraine** with aura and 5.3% of those with **migraine** without aura had consulted a physician. 4) Migraineurs consume significantly more fatty/oily foods, coffee, and tea than nonheadache subjects of the same community. Migraineurs consume significantly fewer fish than nonheadache residents. As a conclusion, only a few Japanese migraineurs receive benefits of medical services and recent advances of headache medicine. The Japanese guideline for chronic headache treatment has declared in 2002. The International Classification of headache disorders has reedited to the 2nd edition. Public education concerning headaches is one of the most urgent issues in Japan. [Abstract]

Richter F, Mikulik O, Ebersberger A, Schaible HG

Noradrenergic agonists and antagonists influence migration of cortical spreading depression in rat-a possible mechanism of migraine prophylaxis and prevention of postischemic neuronal damage.

J Cereb Blood Flow Metab. 2005 Sep;25(9):1225-35.

Cortical spreading depression (CSD) is thought to be a neuronal mechanism that expands the penumbra zone after focal brain ischemia and that causes **migraine** aura. Both adrenergic agonists and antagonists significantly influence the size of the penumbra zone and decline the frequency of **migraine**. To study whether these compounds act by influencing CSD, we applied different drugs topically to an area of the exposed cortex of anesthetized adult rats and observed the migration of CSD-related DC potential deflections across the treated area. The adrenergic agonist norepinephrine (1 mmol/L) and the alpha(2)-agonist clonidine (0.56 mmol/L) blocked reversibly the migration of CSD. The beta-blocker propranolol (250 micromol/L to 1 mmol/L) dose-dependently diminished migration velocity or even blocked migration of CSD. The CSD blockade by the alpha(2)-antagonist yohimbine (1.75 mmol/L) was because of its action on inhibitory 5-HT(1A) receptors. None of the substances in the concentrations used had influence on regional cerebral blood flow or on systemic arterial blood pressure. The data suggest that the interference of these compounds with CSD may contribute to their beneficial therapeutic effect. The effect of beta-receptor antagonists in human **migraine** needs further exploration, since these drugs also work in **migraine** without aura. [Abstract]

Arulmozhi DK, Veeranjaneyulu A, Bodhankar SL

Migraine: current concepts and emerging therapies.

Vascul Pharmacol. 2005 Sep;43(3):176-87.

Migraine is a recurrent incapacitating neurovascular disorder characterized by attacks of debilitating pain associated with photophobia, phonophobia, nausea and vomiting. **Migraine** affects a substantial fraction of world population and is a major cause of disability in the work place. Though the pathophysiology of **migraine** is still unclear three major theories proposed with regard to the mechanisms of **migraine** are vascular (due to cerebral vasodilatation), neurological (abnormal neurological firing which causes the **spreading** depression and **migraine**) and neurogenic dural inflammation (release of inflammatory neuropeptides). The modern understanding of the pathogenesis of **migraine** is based on the concept that it is a neurovascular disorder. The drugs used in the treatment of **migraine** either abolish the acute **migraine** headache or aim its prevention. The last decade has witnessed the advent of Sumatriptan and the 'triptan' class of 5-HT1B/1D receptor agonists which have well established efficacy in treating **migraine**. Currently prophylactic treatments for **migraine** include calcium channel blockers, 5-HT2 receptor antagonists, beta adrenoceptor blockers and gamma-amino butyric acid (GABA) agonists. Unfortunately, many of these treatments are non specific and not always effective. Despite such progress, in view of the complexity of the etiology of **migraine**, it still remains undiagnosed and available therapies are underused. In this article, the diverse pieces of evidence that have linked the different theories of **migraine** with its pathophysiology are reviewed. Furthermore, the present therapeutic targets and futuristic approaches for the acute and prophylactic treatment of **migraine**, with a special emphasis to calcitonin gene-related peptide, are critically evaluated. [Abstract]

Akerman S, Goadsby PJ

Topiramate inhibits cortical spreading depression in rat and cat: impact in migraine aura.

Neuroreport. 2005 Aug 22;16(12):1383-7.

Cortical spreading depression is thought to be the pathophysiological correlate of the neurological symptoms in **migraine** with aura. Topiramate is an anti-epileptic drug that is also used as a **migraine** preventive. Ion homeostasis and excitatory amino acid efflux are major components of **cortical spreading** depression; so given the broad range of actions of topiramate, we examined its effect on **cortical spreading** depression. **Cortical spreading** depression was elicited by a needle stick in the cortex in surgically prepared rats and cats; laser Doppler probes were used to measure the cerebral blood flow and a recording electrode was used to measure electrical nerve cell activity. Topiramate at 30 mg kg(-1) was able to inhibit regional cerebral blood flow changes and **cortical** depolarization and **spreading** depression in all rats, and in 8 of 13 cats. We conclude that topiramate may act on mechanisms involved in the initiation and propagation of **spreading** depression, and that these mechanisms may be similar to those involved in the therapeutic role. [Abstract]

Pietrobon D

Migraine: new molecular mechanisms.

Neuroscientist. 2005 Aug;11(4):373-86.

Migraine is an episodic headache disorder affecting more than 10% of the general population. **Migraine** arises from a primary brain dysfunction that leads to activation and sensitization of the trigeminovascular system. A major incompletely understood issue in the neurobiology of **migraine** concerns the molecular and cellular mechanisms that underlie the primary brain dysfunction and lead to activation and sensitization of the trigeminovascular system, thus generating and maintaining **migraine** pain. Here the author reviews recent discoveries that have advanced our understanding of these mechanisms toward a unifying pathophysiological hypothesis, in which **cortical spreading** depression (CSD), the phenomenon underlying **migraine** aura, assumes a key role. In particular, the author discusses the main recent findings in the genetics and neurobiology of familial hemiplegic **migraine** and the insights they provide into the molecular and cellular mechanisms that may lead to the increased susceptibility of CSD in migraineurs. [Abstract]

Bolay H, Moskowitz MA

The emerging importance of cortical spreading depression in migraine headache.

Rev Neurol (Paris). 2005 Jul;161(6-7):655-7.

Migraine is a disabling neurovascular disorder with a complex pathophysiology. Functional imaging and magneto encephalographic studies strongly suggest that **Cortical Spreading** Depression (CSD) constitutes the biological basis for the neurologic aura that precedes headache in one fourth of migrainers. It is likely that the aura is the generator of the headache since experimentally, CSD triggers the activation of the trigeminovascular system, possibly through matrix metalloproteases activation which is associated with an increase in vascular permeability. These data may have therapeutic implications: strategies to block trigeminal activation or its downstream consequences are central to treat the acute headache whereas strategies to block events lying upstream of trigeminal activation would be crucial in prophylaxis. [Abstract]

Koroleva VI, Davydov VI, Roshchina GIa

[Suppression of gamma EEG activity as an index of a spreading depression wave in the neocortex of a waking rabbit]

Zh Vyssh Nerv Deiat Im I P Pavlova. 2005 Jul-Aug;55(4):437-43.

A **spreading** depression (SD) can spontaneously develop in seizures, attacks of **migraine**, vascular disorders and other pathological states of the brain. However, problems in technique of recording the DC-potential in the neocortex of humans and waking animals substantially restrict the possibilities of studying functional consequences of the SD. In this article, the EEG pattern was studied in detail at the moment of the SD development. Specific features were revealed, which make it possible to detect the SD without recording shifts of the DC-potential. At the moment of the SD arrival, the interhemispheric balance drastically disturbs because of a strong decrease in the high-frequency activity. By the time indices, the course of the suppression of the gamma1 and gamma2 EEG frequencies is the most reliable symptom of the SD wave development. The EEG spectral power in the delta band increases with a certain delay in reference to the deep depression of the high-frequency activity and is, in essence, an SD aftereffect. The found EEG signs of an SD wave can substantially simplify the identification of this phenomenon both in experiment and clinical conditions in certain pathological states of the brain. [Abstract]

Edvinsson L, Uddman R

Neurobiology in primary headaches.

Brain Res Brain Res Rev. 2005 Jun;48(3):438-56.

Primary headaches such as **migraine** and cluster headache are neurovascular disorders. **Migraine** is a painful, incapacitating disease that affects a large portion of the adult population with a substantial economic burden on society. The disorder is characterised by recurrent unilateral headaches, usually accompanied by nausea, vomiting, photophobia and/or phonophobia. A number of hypothesis have emerged to explain the specific causes of **migraine**. Current theories suggest that the initiation of a **migraine** attack involves a primary central nervous system (CNS) event. It has been suggested that a mutation in a calcium gene channel renders the individual more sensitive to environmental factors, resulting in a wave of **cortical spreading** depression when the attack is initiated. Genetically, **migraine** is a complex familial disorder in which the severity and the susceptibility of individuals are most likely governed by several genes that vary between families. Genom wide scans have been performed in **migraine** with susceptibility regions on several chromosomes some are associated with altered calcium channel function. With positron emission tomography (PET), a **migraine** active region has been pointed out in the brainstem. In cluster headache, PET studies have implicated a specific active locus in the posterior hypothalamus. Both **migraine** and cluster headache involve activation of the trigeminovascular system. In support, there is a clear association between the head pain and the release of the neuropeptide calcitonin gene-related peptide (CGRP) from the trigeminovascular system. In cluster headache there is, in addition, release of the parasympathetic neuropeptide vasoactive intestinal peptide (VIP) that is coupled to facial vasomotor symptoms. Triptan administration, activating the 5-HT

(1B/1D) receptors, causes the headache to subside and the levels of neuropeptides to normalise, in part through presynaptic inhibition of the cranial sensory nerves. These data suggest a central role for sensory and parasympathetic mechanisms in the pathophysiology of primary headaches. The positive clinical trial with a CGRP receptor antagonist offers a new promising way of treatment. [Abstract]

Haan J, Kors EE, Vanmolkot KR, van den Maagdenberg AM, Frants RR, Ferrari MD

Migraine genetics: an update.

Curr Pain Headache Rep. 2005 Jun;9(3):213-20.

A growing interest in genetic research in **migraine** has resulted in the identification of several chromosomal regions that are involved in **migraine**. However, the identification of mutations in the genes for familial hemiplegic **migraine** (FHM) forms the only true molecular genetic knowledge of **migraine** thus far. The increased number of mutations in the FHM1 (CACNA1A) and the FHM2 (ATP1A2) genes allow studying the relationship between genetic findings in both genes and the clinical features in patients. A wide spectrum of symptoms is seen in patients. Additional cerebellar ataxia and (childhood) epilepsy can occur in FHM1 and FHM2. Functional studies show a dysfunction in ion transport as the key factor in the pathophysiology of (familial hemiplegic) **migraine** that predict an increased susceptibility to **cortical spreading** depression--the underlying mechanism of **migraine** aura. [Abstract]

Buzzi MG, Moskowitz MA

The pathophysiology of migraine: year 2005.

J Headache Pain. 2005 Jun;6(3):105-11.

Migraine is a complex patholophysiology in which both central and peripheral components of the trigeminal pain pathway probably play a significant role, both in the symptoms and signs of the attack and in the mechanisms of action of antimigraine compounds, such as triptans, which constitute the most important therapy for aborting **migraine** pain and possess several mechanisms on 5-HT receptor-mediated actions. The experimental neurogenic inflammation model represents a simple procedure to obtain preliminary information on well characterized receptortargeted drugs. The apparent paradox observed with certain drugs that are shown to be effective in this model but not in clinical trials offers the opportunity to better manipulate structure-activity to obtain the best pharmacological profile using an array of experimental models. The observation that nitric oxide donors induce **migraine**-like pain in migraineours and that nitric oxide plays a pivotal role in the control of several functions in the central nervous system, has prompted the use of such molecules for better understanding the pathophysiology of **migraine** attacks. A link between central and peripheral components of the trigeminal pain pathway is provided by the observation that **cortical spreading** depression in the rat activates trigeminovascular afferents and induces a series of **cortical** meningeal and brainstem events consistent with the development of headache. Studies in humans support the hypothesis that **cortical spreading** depression underlies **migraine**.aura. Therefore, tt is possible that visual, motor or sensory aura might be responsible for the generation of the pain through the above mechanisms. [Abstract]

Tottene A, Pivotto F, Fellin T, Cesetti T, van den Maagdenberg AM, Pietrobon D

Specific kinetic alterations of human CaV2.1 calcium channels produced by mutation S218L causing familial hemiplegic migraine and delayed cerebral edema and coma after minor head trauma.

J Biol Chem. 2005 May 6;280(18):17678-86.

Mutation S218L in the Ca(V)2.1 alpha(1) subunit of P/Q-type Ca(2+) channels produces a severe clinical phenotype in which typical attacks of familial hemiplegic **migraine** (FHM) triggered by minor head trauma are followed, after a lucid interval, by deep (even fatal) coma and long lasting severe cerebral edema. We investigated the functional consequences of this mutation on human Ca(V)2.1 channels expressed in human embryonic kidney 293 cells and in neurons from Ca(V)2.1 alpha(1)(-/-) mice by combining single channel and whole cell patch clamp recordings. Mutation S218L produced a shift to lower voltages of the single channel activation curve and a consequent increase of both single channel and whole cell Ba(2+) influx in both neurons and human embryonic kidney 293 cells. Compared with the other FHM-1 mutants, the S218L shows one of the largest gains of function, especially for small depolarizations, which are insufficient to open the wild-type channel. S218L channels open at voltages close to the resting potential of many neurons. Moreover, the S218L mutation has unique effects on the kinetics of inactivation of the channel because it introduces a large component of current that inactivates very slowly, and it increases the rate of recovery from inactivation. During long depolarizations at voltages that are attained during **cortical spreading** depression, the extent of inactivation of the S218L channel is considerably smaller than that of the wild-type channel. We discuss how the unique combination of a particularly slow inactivation during **cortical spreading** depression and a particularly low threshold of channel activation might lead to delayed severe cerebral edema and coma after minor head trauma. [Abstract]

Kunkler PE, Hulse RE, Schmitt MW, Nicholson C, Kraig RP

Optical current source density analysis in hippocampal organotypic culture shows that spreading depression occurs with uniquely reversing currents.

J Neurosci. 2005 Apr 13;25(15):3952-61.

Spreading depression (SD) involves current flow through principal neurons, but the pattern of current flow over the expanse of susceptible tissues or individual principal neurons remains undefined. Accordingly, tissue and single cell maps made from digital imaging of voltage-sensitive dye changes in hippocampal organotypic cultures undergoing SD were processed via optical current source density analysis to reveal the currents associated with pyramidal neurons. Two distinctive current flow patterns were seen. The first was a trilaminar pattern (420 microm2) that developed with the onset of SD in CA3 pyramidal neurons, in which SD most often began. This initial pattern comprised a somatic current sink with current sources to either side in the dendrites that lasted for seconds extending into the first aspect of the classical "inverted saddle" interstitial direct current waveform of SD. Next, the somatic sink backpropagated at a speed of millimeters per minute into the proximal dendrites, resulting in a reversal of the initial current flow pattern to its second orientation, namely dendritic sinks associated with a somatic source. The latter persisted for the remainder of SD in CA3 and was the only pattern seen in CA1, in which SD was rarely initiated.

This backpropagating SD current flow resembles that of activity-dependent synaptic activation. Retrograde and associative signaling via principal neuron current flow is a key means to affect tissue function, including synaptic activation and, by extension, perhaps SD. Such current-related postsynaptic signaling might not only help explain SD but also neuroprotection and **migraine**, two phenomena increasingly recognized as being related to SD. [Abstract]

Welch KM

Brain hyperexcitability: the basis for antiepileptic drugs in migraine prevention.

Headache. 2005 Apr;45 Suppl 1S25-32.

Abnormal brain excitability may provide the susceptibility for triggering **migraine** attacks. Antiepileptic drugs may diminish neuronal excitability and consequently reduce the frequency of **migraine**. Because **migraine** aura is predominantly visual, hyperexcitability of the occipital cortex has been the focus of investigations. Functional magnetic resonance imaging of the brain and magnetoencephalography provide the most consistent evidence for the role of brain hyperexcitability in **migraine** and confirm that triggering an abnormal electric and metabolic event consistent with the **cortical spreading** depression (CSD) of Leao is anatomically and functionally linked with **migraine** aura symptoms. Future drug discovery should focus on the interface between the excitable cell and the earliest events of CSD. [Abstract]

Gajos A, Jaworska-Chrebelska T, Bogucki A

[Migraine with a combination of aura symptoms as a clinical manifestation of cortical spreading depression]

Neurol Neurochir Pol. 2005 Mar-Apr;39(2):163-5.

The pathomechanism of the **migraine** aura remains unclear. The most probable cause of the aura is **cortical spreading** depression with associated hypoperfusion. Both the **cortical spreading** depression and hypoperfusion begin in the occipital lobes and spread forward slowly (2-3 mm/min) in a wave-like mode along the brain convolutions and cross territories of brain arteries. We present a 24-year-old female patient with a combination of aura symptoms. Each **migraine** attack began with a bright scintillating zig-zag, which crossed the visual field. It was followed by left sided hemiparesthesiae marching from the face to the hand. The last symptom of aura was motor aphasia. Later a unilateral, pulsating headache developed with associated photo- and phonophobia. The stable pattern and duration of aura symptoms in the presented case suggest that the **cortical spreading** depression plays an important role in the pathomechanism of **migraine** with aura. [Abstract]

Gupta VK

Cortical spreading depression is neuroprotective: the challenge of basic sciences.

Headache. 2005 Feb;45(2):177-8; author reply 178. [Abstract]

Bramanti P, Grugno R, Vitetta A, Di Bella P, Muscar` N, Nappi G

Migraine with and without aura: electrophysiological and functional neuroimaging evidence.

Funct Neurol. 2005 Jan-Mar;20(1):29-32.

The neuropathological processes believed to underlie **migraine** with and without aura are still widely debated in the literature. In order to arrive at a more detailed and comprehensive picture of the altered processes present in migraineurs, electrophysiological data obtained through transcranial magnetic stimulation (TMS) and electroencephalography (EEG) were combined with haemodynamic data obtained through functional magnetic resonance imaging (fMRI). Ten subjects affected by **migraine** (with or without aura) underwent TMS and EEG investigation prior to a visual stimulation task, studied in fMRI. Our preliminary results showed a reduced **cortical** silent period especially in subjects affected by **migraine** with aura. The fMRI BOLD response was found to be weaker in occipital areas proportionally to the frequency and severity of **migraine** attacks. The data obtained from our study seem to support the theory of **cortical spreading** depression recently observed in human subjects. Moreover, the electrophysiological data were also correlated to **migraine** attack frequency, thus pointing to elevated **cortical** excitability between attacks. Better understanding of the neuropathological processes that trigger **migraine** attacks will help in the selection of more adequate prophylactic therapies. The results of this preliminary study need to be confirmed in a a large sample of subjects. [Abstract]

Solheim O, Skeidsvoll T

Transient global amnesia may be caused by cerebral vein thrombosis.

Med Hypotheses. 2005;65(6):1142-9.

Transient global amnesia (TGA) is a disorder of unknown aetiology, characterized by sudden loss of anterograde memory, in the absence other neurological signs or symptoms, followed by complete recovery in less than 24h. Precipitating actions such as strenuous physical activity or valsalva-like manoeuvres are frequently reported. Since first described in 1958, by Fisher and Adams, the possible pathophysiology has undergone much speculation. Nonconvulsive epileptic seizures, **migraine**, paradoxical embolism thorough a patent foramen ovale, and transient ischemic attacks have been proposed as potential mechanisms. One of the latest hypotheses is that venous congestion causes either ischemia or induces **spreading** depression in the medial temporal lobes. It has been demonstrated that retrograde flow in the internal jugular veins occurs more frequently during valsalva manoeuvres in TGA patients than in controls, supporting a dysfunctional venous circulation as part of the pathogenesis. However, earlier hypotheses typically fail to explain the relatively low recurrence rate of TGA, lack of comorbidity and the relation to precipitating events. If cerebral venous hypertension was the solely cause of TGA it would presumably be much more common with very high recurrence rates among those predisposed of the condition. Structural changes observed in MRI and SPECT studies along with reports of mild cognitive impairment lasting much longer than the amnestic episodes, indicate that TGA is less transient and perhaps somewhat less benign than earlier believed. Many cases of TGA seem to be associated with factors of increased risk of cerebral venous thrombosis, such as polycythemia, antiphospholipid antibodies, venous hypertension, female sex and more. We suggest that most cases of TGA may be due to small thrombi in the deep cerebral venous system. Small venous thrombi may difficult to visualize even when using modern imaging technology. Further studies of TGA patients with for example blood analysis of D-dimer together with MR venography or CT

venography could be done to evaluate this new hypothesis. [Abstract]

Mackert BM

The discovery of slowness--recent progress in DC-MEG research.

Neurol Clin Neurophysiol. 2004;200441.

The non-invasive electrical recording of Direct Current (DC) phenomena in the frequency range below 0.1 Hz, e.g., occurring in metabolic injuries to brain cells in stroke or **migraine** (anoxic depolarization, peri-infarct depolarization, **spreading** depression), is technically restricted due to large drift artifacts caused by electrochemical instabilities at the electrode-skin interface. This limitation could be overcome by invasive approaches only. However, as early as 1969 first magnetic fields in this frequency range have been recorded over the human torso by oscillating the subject vertically in front of a magnetic field detector using a see-saw. By this technique the DC field is conversed to a higher frequency, where the external noise level is less. In the last decade, the modulation based DC-magnetoencephalography (DC-MEG) has been methodically refined, which allowed monitoring low-amplitude magnetic fields in this frequency domain arising not only from injured tissue, but also generated by functional **cortical** activation. Furthermore, the combination of DC-MEG and NearInfraRed Spectroscopy (NIRS) opens up a new avenue to study **cortical** neurovascular coupling, as vascular and neuronal activations could be analyzed simultaneously even without averaging in a single-trial mode. Recordings inside the novel magnetically shielded room (BMSR-2 of the Physikalisch-Technische Bundesanstalt, Berlin) exhibiting an extremely low background noise level in the DC frequency range, and alleviating the need of sensor-to-source modulation, allow to resolve additionally the short-term (subsecond) dynamics of neuronal DC-processes. [Abstract]

Tvedskov JF, Iversen HK, Olesen J

A double-blind study of SB-220453 (Tonerbasat) in the glyceryltrinitrate (GTN) model of migraine.

Cephalalgia. 2004 Oct;24(10):875-82.

The need for experimental **migraine** models increases as therapeutic options widen. In the present study, we investigated SB-220453 for efficacy in the glyceryltrinitrate (GTN) human experimental **migraine** model. SB-220453 is a novel benzopyran compound, which in animal models inhibits neurogenic inflammation, blocks propagation of **spreading** depression and inhibits trigeminal nerve ganglion stimulation-induced carotid vasodilatation. We included 15 patients with **migraine** without aura in a randomized double-blind crossover study. SB-220453 40 mg or placebo was followed by a 20-min GTN infusion. Headache, scored 0-10, was registered for 12 h, and fulfillment of International Headache Society (IHS) criteria was recorded until 24 h. Four subjects had a hypotensive episode after SB-220453 plus GTN but none after GTN alone. The reaction was unexpected, since animal models and previous human studies had shown no vascular or sympaticolytic activity with SB-220453. The study was terminated prematurely due to this interaction. GTN was consistent in producing headache and **migraine** that resembled the patients' usual spontaneous **migraine**. Nine patients had GTN on both study days. Peak headache score showed a trend towards reduction after SB-220453 compared with placebo (median 4 vs. 7, P = 0.15). However, no reduction was seen in the number of subjects experiencing delayed headache (8 vs. 8), number of subjects reporting **migraine** (6 vs. 8), **migraine** attacks fulfilling IHS criteria 1.1 or 1.7 (6 vs. 7) or IHS 1.1 alone (4 vs. 5). SB-220453 had no significant pre-emptive anti-**migraine** activity compared with placebo in this human model of **migraine**. Interaction between SB-220453 and GTN was discovered. This is important for the future development of the compound and underlines the usefulness of experimental **migraine** models. [Abstract]

Parsons AA

Cortical spreading depression: its role in migraine pathogenesis and possible therapeutic intervention strategies.

Curr Pain Headache Rep. 2004 Oct;8(5):410-6.

Cortical spreading depression (CSD) is a well-characterized phenomenon in experimental animals. Recent data show that CSD actually can occur in the injured human brain and compelling evidence is accumulating to support the concept that CSD is responsible for **migraine** aura. The aim of this review is to highlight recent key advances regarding our understanding of CSD in animal and human studies and its relevance to the pathophysiology of **migraine** and its potential treatment options. [Abstract]

Faria LC, Mody I

Protective effect of ifenprodil against spreading depression in the mouse entorhinal cortex.

J Neurophysiol. 2004 Oct;92(4):2610-4.

In the brain, **spreading** depression (SD) is characterized by a large extracellular DC shift, a massive failure of ion homeostasis and a transient cessation of neuronal function. Clinically, SD is believed to be involved in various neurological disorders including **migraine** and cerebrovascular diseases. The propagation of **cortical** SD requires the release of glutamate, and N-methyl-D-aspartate (NMDA) receptors play a crucial role in this process. Here, we have isolated the NMDA receptor-mediated component of extracellularly recorded field excitatory postsynaptic potentials (fEPSPs) in layers 2-3 of the entorhinal cortex of murine brain slices. In the absence of GABAA and AMPA receptor-mediated synaptic transmission, stimulation of layer 6 afferents every 15-90 s elicited spontaneous SD on average within 18.5 min after the start of the stimulation. In the presence of ifenprodil, an NR2B receptor subunit-selective NMDA receptor antagonist, the occurrence of SD was nearly abolished. Our results are consistent with an important role of NR2B subunits in triggering SD in the entorhinal cortex. [Abstract]

Montagna P

The physiopathology of migraine: the contribution of genetics.

Neurol Sci. 2004 Oct;25 Suppl 3S93-6.

Recent advances in the studies of the genetic liability to **migraine** include the discovery of two genes responsible for familial hemiplegic **migraine** (FHM) and the analysis of several sites of linkage or genetic association for the so-called typical migraines, e. g., **migraine** with (MA) and without aura (MO). The 2 genes implicated in the genetics of FHM are CACNA1A for FHM1 and ATP1A2 for FHM2. It is still unclear how dysfunction in these genes may trigger attacks of **migraine** with hemiplegic features and, in at least part of the families with FHM,

also paroxysmal or progressive ataxia and epileptic seizures. It appears that mutations in CACNA1A responsible for FHM1 alter calcium influx and calcium currents in neurons, possible factors of **spreading** depression like events. On the other hand, abnormal regulation of intracellular calcium concentrations could alter neurotransmitter release and other cellular functions. In the case of ATP1A2 mutations, haplo-insufficiency of the gene has been hypothesised to result in abnormal potassium level regulation because of faulty Na/K exchange with subsequent depolarisation and increased liability to **spreading** depression, or/and in abnormal calcium levels because of the concomitant activation of the Na/Ca exchanger, with a mechanism therefore comparable to that at work in FHM1. Much more work is clearly necessary to elucidate these pathophysiological mechanisms; advances in genetics however may represent important steps in the clarification of the physiopathology of the **migraine** attack. [Abstract]

Bussone G

Pathophysiology of migraine.

Neurol Sci. 2004 Oct;25 Suppl 3S239-41.

The exact pathogenesis of **migraine** remains to be determined. In particular there is increasing evidence for the neural basis of **migraine**. We now have a body of data supporting the concept of central neuronal hyperexcitability as a pivotal physiological disturbance predisposing to **migraine**. The reasons for increased neuronal excitability may be multifactorial. Most recently, abnormality of calcium channels has been introduced as a potential mechanism of interictal neuronal excitability. Mutant voltage gated P/Q type calcium channel genes likely influence presynaptic neurotransmitter release, possibly of excitatory amino-acid systems or inhibitory. It could therefore be hypothesised that genetic abnormalities result in a lowered threshold of response to trigger factors. There is also evidence from spectroscopic studies that magnesium is low in **migraine**. We currently conceive of a **migraine** attack as originating in the brain. Triggers of an attack initiate a depolarising neuroelectric and metabolic event likened to the **spreading** depression of Leao. This event activates the headache and associated features of the attack by mechanisms that remain to be determined, but appear to involve either peripheral trigeminovascular or brain stem pathways, or both. Excitability of cell membranes, perhaps in part genetically determined, is the brain's route of susceptibility to attacks. Factors that increase or decrease neuronal excitability constitute the threshold for triggering attacks. [Abstract]

Kors EE, Vanmolkot KR, Haan J, van den Maagdenberg AM, Frants RR, Ferrari MD

[From gene to disease; familial hemiplegic migraine as a result of mutations in a sodium-potassium pump gene]

Ned Tijdschr Geneeskd. 2004 Sep 25;148(39):1919-20.

Familial hemiplegic **migraine** (FHM) is a rare, autosomal dominant subtype of **migraine**, associated in half of the families with mutations in the CACNA1A gene located on chromosome 19p13, which encodes the Cav2.1-subunit of brain-specific P/Q-type calcium channels. Recently, mutations in a second gene, ATP1A2 on chromosome 1q23, which encodes a sodium-potassium exchange pump subunit, have been identified. The first functional studies indicate that A TP1A2 FHM mutations result in a loss of function of the pump, leading to an increase in extracellular potassium. This is known to evoke **cortical spreading** depression, the underlying mechanism of **migraine** aura. [Abstract]

Tamura Y, Kataoka Y, Cui Y, Yamada H

Cellular proliferation in the cerebral cortex following neural excitation in rats.

Neurosci Res. 2004 Sep;50(1):129-33.

Cortical spreading depression (SD) is characterized by propagation of neuronal/glial membrane depolarization throughout the unilateral cerebral cortex and has been linked to several neurological disorders, including **migraine** aura and epilepsy. SD induction resulted in a dramatic increase in BrdU-incorporated cells in the ipsilateral **cortical** hemisphere that was dependent on the number of elicited SD. Immunohistochemical studies revealed that 53% of the BrdU-labeled cells in the SD-generated cortex were NG2 immunopositive and 25% were OX-42 immunopositive. The remaining 22% of BrdU-incorporated cells showed no immunoreactivity to GST-rr, GFAP, NeuN, NG2 or OX-42.These data indicate that functional excitation of the cerebral cortex induces proliferative response in **cortical** cells, which may subsequently differentiate into glial progenitor or microglia within 3 days after stimulation. [Abstract]

Straube A, Fvrderreuther S

[Sleeping behaviour and headache attacks in cases of primary headache. Possible pathological mechanisms]

Schmerz. 2004 Aug;18(4):300-5.

Headache is connected with sleep quality, e.g. hypnic headache and chronic paroxysmal headache attacks occur preferentially during REM sleep; this is possibly also true for cluster headache and **migraine**. REM sleep is typically characterized by the occurrence of ponto-geniculo-occipital spikes (PGOs). These PGOs should be able to trigger **cortical spreading** depression (CSD), which, although often clinically silent, is assumed to be an essential element of a **migraine** attack and possibly also of other forms of headache. CSDs are considered a correlate of **migraine** aura. They could lead to the secondary activation of trigeminovascular afferences, which would then induce a headache. Interestingly, illnesses that are comorbid with **migraine** cause an increase in the amount of REM sleep; conversely, various drugs administered prophylactically for these illnesses reduce the quantity of REM sleep. [Abstract]

Hall SD, Barnes GR, Hillebrand A, Furlong PL, Singh KD, Holliday IE

Spatio-temporal imaging of cortical desynchronization in migraine visual aura: a magnetoencephalography case study.

Headache. 2004 Mar;44(3):204-8.

OBJECTIVE: To determine **cortical** oscillatory changes involved in **migraine** visual aura using magnetoencephalography (MEG). BACKGROUND: Visual aura in the form of scintillating scotoma precedes **migraine** in many cases. The involvement of **cortical spreading** depression within striate and extra-striate **cortical** areas is implicated in the generation of the disturbance, but the details of its progression, the effects on **cortical** oscillations, and the mechanisms of aura generation are unclear. METHODS: We used MEG to directly image changes in

cortical oscillatory power during an episode of scintillating scotoma in a patient who experiences aura without subsequent **migraine** headache. Using the synthetic aperture magnetometry method of MEG source imaging, focal changes in **cortical** oscillatory power were observed over a 20-minute period and visualized in coregistration with the patient's magnetic resonance image. RESULTS: Alpha band desynchronization in both the left extra-striate and temporal cortex persisted for the duration of reported visual disturbance, terminating abruptly upon disappearance of scintillations. Gamma frequency desynchronization in the left temporal lobe continued for 8 to 10 minutes following the reported end of aura. CONCLUSIONS: Observations implicate the extra-striate and temporal cortex in **migraine** visual aura and suggest involvement of alpha desynchronization in generation of phosphenes and gamma desynchronization in sustained inhibition of visual function. [Abstract]

Original script provided by Shawn Mikula of BrainMeta.com; modified script created by Shawn Thomas.

Mechanisms of migraine aura revealed by functional MRI in human visual cortex

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Edited by Marcus E. Raichle, Washington University School of Medicine, St. Louis, MO, and approved February 6, 2001 (received for review December 8, 2000)

Cortical spreading depression (CSD) has been suggested to underlie migraine visual aura. However, it has been challenging to test this hypothesis in human cerebral cortex. Using high-field functional MRI with near-continuous recording during visual aura in three subjects, we observed blood oxygenation level-dependent (BOLD) signal changes that demonstrated at least eight characteristics of CSD, time-locked to percept/onset of the aura. Initially, a focal increase in BOLD signal (possibly reflecting vasodilation), developed within extrastriate cortex (area V3A). This BOLD change progressed contiguously and slowly (3.5 ± 1.1 mm/min) over occipital cortex, congruent with the retinotopy of the visual percept. Following the same retinotopic progression, the BOLD signal then diminished (possibly reflecting vasoconstriction after the initial vasodilation), as did the BOLD response to visual activation. During periods with no visual stimulation, but while the subject was experiencing scintillations, BOLD signal followed the retinotopic progression of the visual percept. These data strongly suggest that an electrophysiological event such as CSD generates the aura in human visual cortex.

Migraine is a very common and debilitating disorder. In 20% of cases (1), the migraine headache is preceded by a visual hallucination/illusion known as an aura. Typically, the aura is a serrated arc of scintillating, shining, crenelated shapes, beginning adjacent to central vision and expanding peripherally over 5–20 min, within one visual field, usually followed by headache. The scintillations are followed temporarily by a blind region, after the same retinotopic progression from central to peripheral visual fields.

Leao (2) first suggested a relationship between cortical spreading depression (CSD) and migraine aura, based on the uniquely slow spread of clinical and electrophysiological events. CSD is a wave of neuronal and glial depolarization, followed by long-lasting suppression of neural activity, which is easily evoked in mammals with lissencephalic (2, 3) or folded cortex (4).

Numerous human neuroimaging studies have indirectly suggested that CSD underlies migraine (5). These include planar Xenon (6–9), single photon emission tomography (8, 10–14), positron-emission tomography (15, 16), magnetoencephalography (17, 18), and MRI (19–21). Each demonstrated one or more aspects of CSD associated with migraine aura. However, subjects never experienced symptoms of typical visual auras in studies showing spreading hypoperfusion (15) or blood oxygenation level-dependent (BOLD) signal changes (19), and the initial hyperemia characteristics of CSD have never been directly demonstrated in human cortex. This uncertainty about the mechanisms of migraine visual aura has seriously limited the development of therapeutic drugs that could act directly on CSD.

To detect and follow analogous temporal and spatial events in human visual cortex, we used high-field functional MRI to map the progression of the BOLD events during migraine aura. The BOLD signal is not directly equated with blood flow, rather it reflects the balance between oxygen delivery and oxygen consumption. Nevertheless, changes in BOLD signal intensity have been successfully used in experimental animals to detect the presence of CSD, the rate of CSD propagation, and attendant changes in apparent diffusion coefficients (4). To clarify the topography of the activity spread across cortex, these BOLD events were mapped onto flattened cerebral cortex, in relationship to the retinotopy, in each of three subjects. By so doing, we could identify at least eight fundamental and distinguishing characteristics of CSD in visual cortex during migraine aura in humans, which could not be revealed with previously available techniques.

NEUROBIOLOGY

Patients and Methods

Subjects. We studied three male patients (36 ± 9 years), each fulfilling the International Headache Society criteria for the diagnosis of migraine with aura. A total of five migraine attacks with visual aura were studied. Two were induced in a single patient (P.R.), and three spontaneous migraine episodes were scanned in two other patients (S.R. and M.C.). None were taking prophylactic medication at that time, and none had taken any acute antimigraine drug for at least 1 week before the scan. Informed written consent was obtained for each subject before each scanning session, and all procedures were approved by Massachusetts General Hospital Human Studies Protocol numbers 96–7464 and 93–7253.

General Procedure. Magnetic resonance (MR) data were acquired in a 3-Tesla scanner, using echoplanar imaging. Subjects were scanned by using a bilateral quadrature surface coil. Sixteen contiguous slices, 4 mm thick, were collected in an oblique coronal plane, oriented perpendicular to the calcarine sulcus. The functional scans used the following parameters: gradient echo, echo time = 50 ms, repetition time = 4,000 ms, matrix 128 × 64, in-plane resolution 3.1 × 3.1 mm. Visual stimuli were generated on a Silicon Graphics O2 computer and projected onto the center of a rear projection screen located about 20 cm from the subject's eyes. Face and fixation stimuli subtended 48 × 36° of visual angle. Subjects viewed the screen in a darkened room through a mirror, and corrective lenses were used if necessary.

Subjects fixated the center of a radial flickering checkerboard (2 Hz), which was presented in 16-s epochs (on period), alter-

This paper was submitted directly (Track II) to the PNAS office.

Abbreviations: CSD, cortical spreading depression; BOLD, blood oxygenation level-dependent; MR, magnetic resonance.

†N.H. and M.S.d.R. contributed equally to this work.

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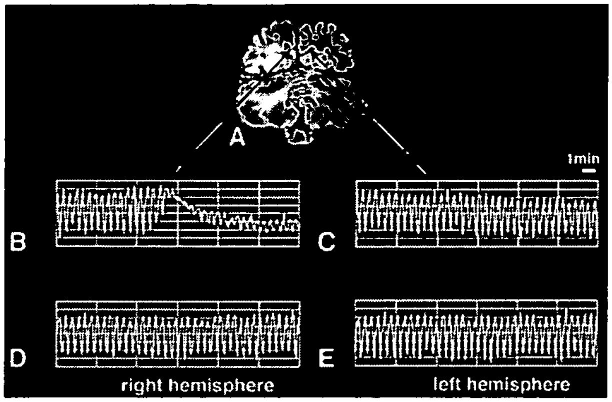

Fig. 1. Ictal and interictal BOLD responses in human visual cortex. A representative functional MRI slice is shown (*A*). The slice plane was oriented near-perpendicular to the calcarine fissure, so that cerebellum occupies the lower portion of the figure, and occipital lobe occupies the upper portion. (*B–E*) Representative BOLD responses over time, taken from single voxels within homologous areas of the occipital lobe (*B* and *D*, *Right* vs. *C* and *E*, *Left*), as designated by green arrows. Time is shown on the *x* axis, and levels of MR modulation are shown on the *y* axis. The stimulus-driven signal oscillation in *B–E* is the BOLD responses to 16-s presentations of the checkerboard visual stimulus (on response), relative to the intervening 16-s presentations of a black screen with a fixation point (off response). (*D* and *E*) Normal BOLD modulation during an interictal period for each hemisphere. (*B* and *C*) The BOLD responses during a migraine aura affecting only the right hemisphere (*B*) (see Fig. 2). Perturbations did not appear in the left hemisphere during the ictal (*C*), or interictal scans (*D* and *E*).

nating with 16-s presentation of a uniform black stimulus (off period), during two consecutive runs. A central fixation point was present at all times. A squeeze bulb was used to record the initiation and termination of the visual aura and headache.

In addition to interictal scans, retinotopic maps of polar angle and eccentricity were generated in the same subjects by using stimuli as described (22–26). To improve topographic clarity, all data were analyzed and displayed in cortical surface format as described (22–26).

Perfusion weighted imaging scans were done at the end of the BOLD imaging during a migraine attack to assess late hemodynamic changes. A standard head coil was used for the perfusion weighted imaging [echoplanar imaging spin echo, 10 axial slices, 51 images/slice, repetition time 1500, echo time 75, 0.2 mmol/kg of Gd-pentaacetic acid at a rate of 5 cc/sec by using a MedRad power injector (MedRad, Pittsburgh, PA)].

Experimental Design. *Triggered case.* Immediately before each of the imaging studies, our subject (P.R.) reproduced those conditions known in the past to induce his migraine attack. After ≈80 min of continuous basketball playing, when the patient considered that the level of exercise was adequate to trigger an attack, he was taken to the MRI facility, and BOLD imaging was started before any visual symptom was present. The patient was instructed to press a squeeze bulb on three different occasions to indicate (*i*) the beginning of the visual aura, (*ii*) the end of the visual aura, and (*iii*) the beginning of headache.

Each scan consisted of 512 images/slice, lasting 34 min, 8 s. Two scans were done per session, and a total of three scanning sessions were done. In two scanning sessions, the subject developed stereotypical migraine with visual aura. On a third scan session done under the same conditions, the patient did not have any symptoms (visual aura or pain).

Subject P.R. described the visual aura as a scintillating white noise ("like TV snow") beginning in the paracentral left visual field. The boundary of the scintillations was well defined. The aura had an expanding crescent shape, progressing slowly outward, with a minor clockwise component, affecting the lower quadrant to a greater extend early on. The white noise was closely followed by a scotoma that persisted in the center of the visual field for a few minutes. The scintillations plus the scotoma moved from the center of vision toward the periphery over 22–27 min. While the vision was still abnormal a mild throbbing headache began contralateral to the hemifield defect.

The other two spontaneous cases described similar visual symptoms lasting between 25 and 35 min, followed by either a bilateral occipital (subject S.R.) or frontotemporal headache contralateral to the hemifield defect (subject M.C.).

Spontaneous cases. Patients suffering from migraine with visual aura contacted us as soon as possible after the initiation of

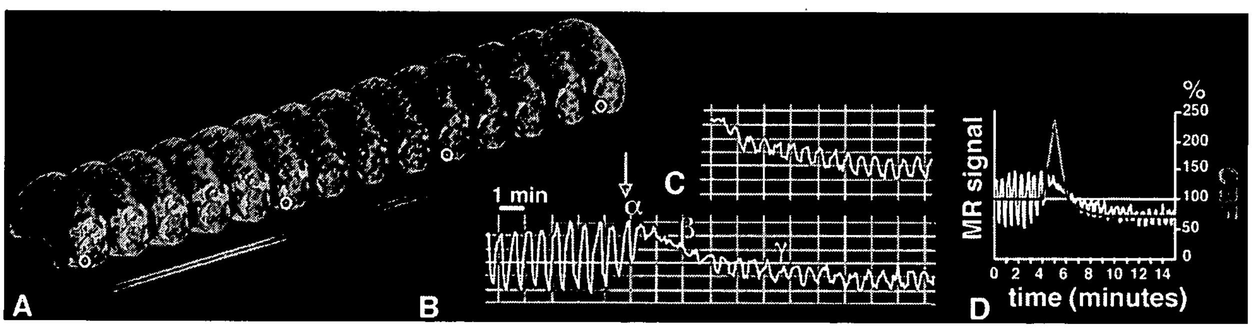

Fig. 2. Time-dependent BOLD activity changes from a single region of interest in VI, acquired before and during episodes of either spontaneous (*C*) or induced (*B*) visual aura. (*A*) A series of anatomical images, including BOLD activity on "inflated" cortical hemispheres showing the medial bank (similar to a conventional midsagittal view). Images were sampled at 32-s intervals, showing the same region of interest (circles) in V1. (*B*) The MR signal perturbation over time from the circled region of interest; the perturbation is similar to that in Fig. 1*B*. Variations in time are color-coded (deep red to magenta), and the four colored circles match corresponding times within the V1 region of interest. The slice prescription failed to include a few mm in the most posterior part of the occipital pole in that induced attack, so activation is not revealed in any of these images. *B* shows that before the onset of the aura, the BOLD response to visual stimulation shows a normal, oscillating activation pattern. After the onset of aura (green arrow), the BOLD response showed a marked increase in mean level (α), a marked suppression to light modulation (β), followed by a partial recovery of the response to light modulation at decreased mean level (γ; −3% to −6%). (*C*) Data from a spontaneous attack (subject M.C.), captured ≈18 min after the onset of the visual symptoms affecting the right hemifield. The data represent the time course in left visual area V1, at an eccentricity of ≈20° of visual angle. (*D*) A superimposition of CBF changes seen in the rat during CSD (as described by Lauritzen *et al.* in ref. 46) with the MR signal data shown in *A*. Note that the timing of the hyperemia (3–4.5 min in CSD vs. 3.3 ± 1.9 min in migraine aura) is remarkably similar in these two quite different data sets. The amplitude of the hyperemia is different in the two conditions, presumably because of differences in the blood flow measurement techniques used (laser doppler versus BOLD) and the nonlinear relationship between blood flow and BOLD signal.

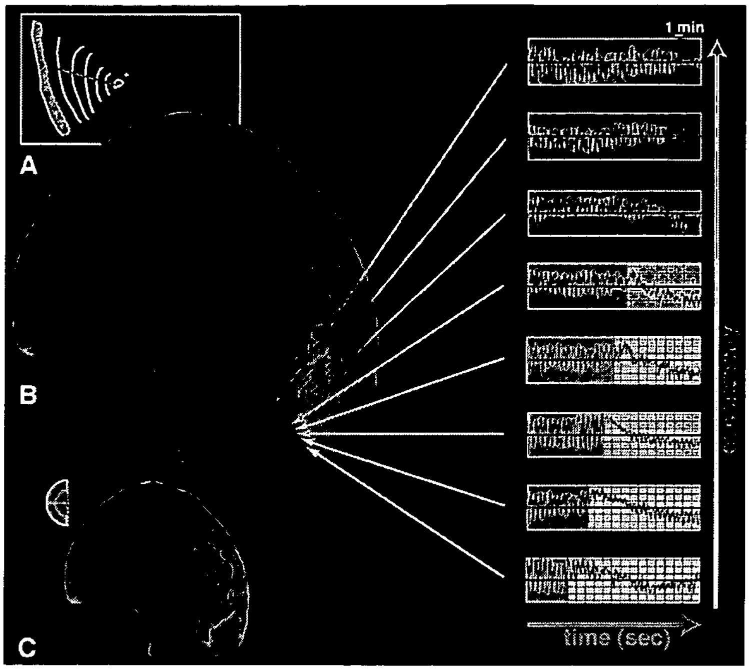

Fig. 3. Spreading suppression of cortical activation during migraine aura. (*A*) A drawing showing the progression over 20 min of the scintillations and the visual field defect affecting the left hemifield, as described by the patient (P.R.). The fixation point appears as a small white cross. The red line shows the overall direction of progression of the visual percept. The front of the scintillation at different times within the aura is indicated by a white line. (*B*) A reconstruction of the same patient's brain (P.R.), based on anatomical MR data. The posterior medial aspect of occipital lobe is shown in an inflated cortex format. In this format, the cortical sulci and gyri appear in darker and lighter gray, respectively, on a computationally inflated surface. MR signal changes over time are shown to the right. Each time course was recorded from one in a sequence of voxels that were sampled along the calcarine sulcus, in the primary visual cortex (V1), from the posterior pole to more anterior location, as indicated by arrowheads. A similar BOLD response was found within all of the extrastriate areas, differing only in the time of onset of the MR perturbation The MR perturbations developed earlier in the foveal representation, compared with more eccentric representations of retinotopic visual cortex. This finding was consistent with the progression of the aura from central to peripheral eccentricities in the corresponding visual field (*A* and *C*). (*C*) The MR maps of retinotopic eccentricity from this same subject, acquired during interictal scans. As shown in the logo in the upper left, voxels that show retinotopically specific activation in the fovea are coded in red (centered at 1.5° eccentricity). Parafoveal eccentricities are shown in blue, and more peripheral eccentricities are shown in green (centered at 3.8° and 10.3°, respectively).

visual symptoms. Because the subjects worked in the same building as the MRI facility, they could be placed in the magnet within 15–20 min after onset. The protocol included a BOLD study followed by perfusion weighted imaging scans. Patients were instructed to indicate to indicate first the end of the visual aura, and then the beginning of headache, using the squeeze bulb.

Duration of each of the imaging BOLD scans for subject S.R. and subject M.C. (one/attacks) was 34 min, 8 s. The second attack of subject M.C. was imaged during three scans of 8 min, 34 s.

Image Processing and Statistical Analysis. MR time courses (Figs. 1–3) were analyzed by using a standard *t*-statistic, computing the difference between the activation amplitude during the off period preceding the aura, compared with each of the on (Fig. 2) and off periods throughout the scanning session. MR time courses were extracted independently from voxels within specific visual areas, and/or at specific eccentricities (Figs. 3 and 5).

To detect the source of the signal change, we analyzed the time course of each voxel individually, analyzing only the voxels that were significantly ($P > 0.01$) activated. A reference baseline (mean MR signal amplitude) and SD were computed on the six first cycles (before the beginning of the aura). Then, pixels which exhibited, at a given latency, (*i*) a mean MR signal higher than the reference mean plus the reference SD and (*ii*) a SD less than the reference SD were coded as positive, if this change lasted for at least two cycles. The value represented is the beginning of the signal change in the positive voxels as defined above.

Results

Three patients were investigated during five episodes of visual aura. In one case (subject P.R.), the attacks were triggered by exercise, and data were acquired before, during the aura, and in the headache phase in two episodes. In the other two migraineurs (M.C. and S.R.), spontaneous auras were captured 15–20 min after onset, and imaging acquisition continued into the headache phase.

Interictal Studies. Interictal studies were performed in the three migraineurs and in seven healthy, age-matched male volunteers. All subjects showed the same pattern of activation of the visual cortex, and no difference was observed between migraineurs and nonmigraineurs. During continuous BOLD imaging (scan duration = 34 min, 8 s), the amplitude of the activation elicited by the checkerboard presentation remained constant (Fig. 1 *D* and *E*).

In the inducible patient, exercise failed to trigger the migraine attack in one of the trials. The MR findings during that nonmigrainous trial were comparable to those obtained in the interictal studies in migraineurs and nonmigraineurs.

Induced Attacks. In both attacks of migraine with visual aura, the BOLD signal changes were similar and were restricted to the occipital cortex contralateral to the visual aura (Fig. 1). Before

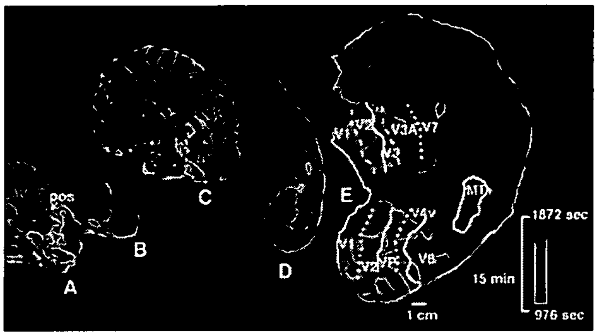

Fig. 4. Source localization and time of onset of the MR signal perturbations. (*A* and *C*) The data on (normally) folded right hemispheric cortex; (*B* and *D*) the same data on inflated cortical surface (as in Figs. 2 and 3). (*E*) A fully flattened view of the cortical surface, as shown in previous publications (24–26, 37, 53). (*A* and *B*) A view of the exposed medial bank from the posterior pole. (*C* and *D*) Shown is the entire hemisphere, from a posterior-medial view. Pos indicates the parieto-occipital sulcus. As described in Fig. 2, activation data were not acquired from the extreme posterior tip of the occipital pole. Cortical locations showing the first BOLD perturbations are coded in red (*E*). Locations showing the BOLD perturbations at progressively later times are coded by green and blue (see pseudocolor scale to the right). The aura-related changes appeared first in extrastriate cortex (V3A, closely followed by V3 and V2), then progressed into V1. The spread of the aura began, and was most systematic, in the representation of the lower visual field (upper bank), becoming less regular as it progressed into the representation of the upper visual field.

the onset of the aura, the BOLD signal showed a stereotypical, normal response, consisting of an increase in BOLD signal during the checkerboard presentation, followed by a decrease in signal when the screen was black (Fig. 1 *D* and *E*). Only after the onset of scintillations (signaled by the subject, see above) did the BOLD response deviate from this stereotypical pattern.

The first changes consisted of an increase in the mean MR signal (5 ± 1.5%) and a decrease of the amplitude of the signal oscillation (duration = 3.3 ± 1.9 min). These initial BOLD features are consistent with the initial features of the aura percept. That is, increases in visual activity (scintillations) occur during increases in the mean BOLD levels. Furthermore, those same scintillations (which overlie existing visual stimuli) are paralleled by decreases in the stimulus-driven MR oscillations (Fig. 2*B*, α).

These initial changes were followed by a decrease in the mean MR signal (5 ± 0.7%) (Fig. 2*B*, β and γ) whereas the stimulus-induced response remained suppressed. Perceptually, this phase appears to correspond to the localized scotoma. Both the mean MR signal and the stimulus-induced response recovered slowly (to 80% of initial level by 15 ± 3 min), following the same sequence as the suppression of stimulus-induced response (see below).

Perfusion weighted images taken at 60–111 min after attack onset showed a decrease in regional cerebral blood flow, regional cerebral blood volume, and an increase in mean transit time in the occipital cortex—where the BOLD changes described above were observed, confirming the results previously published from one of our studies (21).

If these BOLD changes are mechanistically linked to the aura percept, the signal changes should progress systematically across the visual cortical gray matter in accord with the underlying retinotopic maps in the same tissue. This topographic hypothesis was tested by using a flattened cortical format. The retinotopic progression of the BOLD perturbations was systematic and consistent with the migration of visual aura from central to peripheral visual fields. After the onset of the perceptual scintillations, the BOLD signal complex progressed systematically

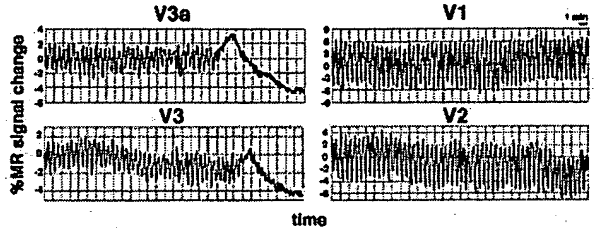

Fig. 5. Time-course evidence for a migraine origin in visual area V3A, taken from the same subject (P.R.) illustrated in Fig. 6, but in a different migraine attack. The slice prescription did include the most posterior part of the occipital pole. Each of the four panels shows the BOLD signals from a voxel in either area V3A, or V3, or V2 or V1. All voxels were sampled from approximately equivalent (parafoveal) retinotopic eccentricities. Time is represented along the *x* axis, and the range is equal and synchronized in each of the four panels. MR amplitude (indicated on the *y* axis) varied slightly in the different pixels and visual areas. Area V3A showed the first BOLD perturbation. Within a few minutes, the perturbation spread into adjacent area V3. The perturbations then spread further posteriorly into areas V2 and V1—but in those areas, the perturbations occurred at times following the time range shown.

from the posterior pole (where central visual fields are represented), toward more anterior regions representing peripheral visual fields (Figs. 2 and 3).

In a signal source analysis, we found BOLD signal changes developed first in extrastriate cortex (area V3A), in subject P.R (see Fig. 4). These early changes were confirmed during a second attack (Fig. 5). To examine the correspondence between the spreading BOLD events in this study, compared with the velocity of the CSD in previous animal experiments, the rate of signal migration was calculated precisely in the flattened cortex. The average velocity was 3.5 ± 1.1 mm/min, measured along the cortical surface from to its point of origin in V3A. Although our stimulus activated cortex as far anteriorly as the precuneus, the spreading BOLD perturbation did not cross the parieto-occipital gyrus (see Fig. 4); in this sense it matches the predictions from the CSD literature (27). However, our MR perturbations did cross cytoarchitectonic boundaries transparently, such as the prominent one between V1 and V2 (see Fig. 3). As one would expect from CSD, temporo-spatial aspects of our BOLD changes

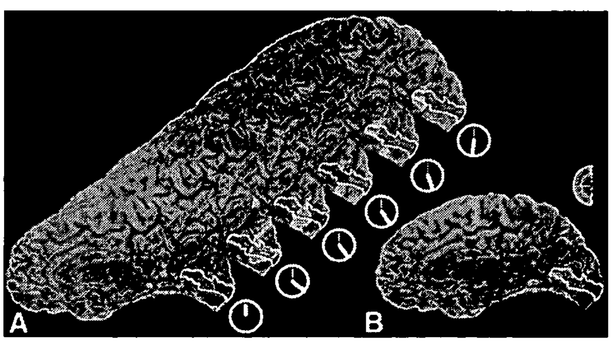

Fig. 6. Progression of the scintillations in the dark, without the flickering checkerboard stimuli. (*A*) A series of images of the brain of the subject at different times, from the beginning of the scanning session (see the little clocks below). The primary visual cortex lies within the white line. Initially, no activation can be seen in V1. However, with the subjective apparition of the scintillations (after 20 min, see clock), activation appears in V1, that progresses from the foveal representation of the visual field to more peripheral representations, paralleling the progression of the scintillations described by the subject. (*B*) A medial view of the subject's brain with the MR maps of retinotopic eccentricity acquired during interictal scans. (see above, Fig. 3).

did not fit simply within any known arterial or venous macrovascular territory.

Spontaneous Attacks. Three spontaneous attacks were captured in two subjects within 15–20 min of the onset of visual symptoms. These BOLD data revealed a decrease in the amplitude and the mean MR signal (Fig. 2*A*). The observed changes were similar to these in the induced attack, when comparisons were made at similar latencies after the aura onset. Because the attacks were spontaneously generated and therefore unpredictable, no baseline (BOLD signal previous to visual symptoms) was available in the spontaneous attacks. Therefore, we could not quantify the percentage decrease in the amplitude or recovery, as was possible in induced attacks. Nevertheless, similarities between the BOLD signal perturbations in five induced and spontaneous attacks (decreased amplitude and mean MR signal, temporal pattern of signal recovery, and retinotopic congruence to the visual percept) suggest that our findings are likely to be generalizable to a much larger population of migraineurs with visual aura.

Scintillation Percept in the Dark. In the triggered case, we also examined the BOLD signal during the off periods (Fig. 6). As expected, no signal was present during these periods before the beginning of the symptoms. However, with the subjective apparition of scintillations described by the subject, one could observe a BOLD signal change appearing first in area V3A and then progressing congruently with the retinotopic percept.

Discussion

Our data confirmed previous reports that CSD-like phenomena can be seen with neuroimaging techniques (7, 10, 12, 15, 19, 20, 28). Like those previous studies, our data indicated a slowly spreading area of abnormal blood flow in the occipital lobe during migraine aura.

Here, we extended these important studies in a number of ways. Within the same attack, and using analytical techniques that enhanced both the spatial and temporal resolution, we measured the retinotopic nature of the observed BOLD signal changes. This approach revealed at least eight neurovascular events in the occipital cortex that resemble cortical spreading depression: (*i*) an initial cortical gray hyperemia, with (*ii*) a characteristic duration, and (*iii*) a characteristic velocity, which (*iv*) is followed by hypoperfusion, and shows (*v*) an attenuated response to visual activation, and (*vi*) a recovery to baseline mean level, and (*vii*) a concurrent recovery of the stimulus-driven activation. Finally (*viii*), we found that (like CSD) the spreading phenomenon did not cross prominent sulci (e.g., the parieto-occipital sulcus).

An increase in the mean MR signal and a decrease of stimulus-driven modulation were the first BOLD signal changes in subject P.R. The most likely source of those initial responses was an increase in blood flow and volume caused by heightened neural activity reflected perceptually by the shining, scintillating migrating visual aura.

Alternative interpretations could be offered, but those seem less likely to us. For instance, the mean MR signal increase could reflect low oxygen consumption, due to decreased neural activity with (uncoupled) constant blood flow. However, the scintillating percept appears to reflect increased (rather than decreased) neural activity—so this interpretation does not seem likely.

Another possible interpretation is that venoconstriction could increase the mean BOLD level. However, by this hypothesis, the resultant blood volume decrease presumably would be outweighed by the associated increase in blood flow (29–31). The initial increase in BOLD signal is also inconsistent with a vasospasm; instead the early increase suggests flow changes driven by neural and metabolic demands.

It has not been clear whether a specific region in occipital lobe initiates the spreading event. Some have attributed the visual phenomena to primary visual cortex (32, 33), because the visual image is oriented and highly retinotopic, and striate cortex is also retinotopic and selective for oriented stimuli (34–37). However, human occipital cortex is comprised of multiple cortical areas, many of which (like V1) are also retinotopic (24–26, 37–39) and orientation-selective (e.g., ref. 37). Hence, the auras could arise from many of these extrastriate areas (e.g., V2, V3/VP, V3A, V4v), as well as V1.

We found that area V3A first developed BOLD signal changes in subject P.R. These early changes were confirmed during a second attack (Fig. 5). Such extrastriate foci are consistent with prior reports (15). V3A is especially sensitive to both motion and luminance contrast (26), and aberrant neuronal firing in this location might well produce scintillations like those described by migraineurs during a typical visual aura. Moreover, area V3A is retinotopic, and it has a continuous representation of a whole hemifield, which is again consistent with the progression of a typical migraine aura.

Because source analysis could not be performed in all attacks, additional studies will be necessary to establish the relationship between area V3A and the onset of prototypical visual auras. Other types of migraine aura, e.g., those containing corrugated lines (the "fortress illusion") might initiate in area V1, whereas those containing colored phosphenes, might reflect a focus in area V8, a color-selective area (24). Somaesthetic auras might well originate in somatosensory cortex. Whether such cortical areas possess a unique density or distribution of calcium channels, as mutated in some patients with familial hemiplegic migraine (40), remains to be studied.

Short of electrophysiological measurements, the present high-resolution imaging suggests that CSD within human occipital cortex explains the spatial and temporal characteristics of the migraine visual aura. CSD is characterized by initial hyperemia lasting 3–4.5 min (4, 6, 7, 41–44) (see Fig. 2*C*). The hyperemia is then followed by a mild hypoperfusion (6, 18, 19, 45–51) lasting 1–2 h—not unlike what was described many minutes after the aura in human occipital cortex (7, 10, 15, 20, 21).

Convergent data suggest that migraineurs may be especially susceptible to slowly spreading excitable events within cerebral cortex (19). First, the slow rate of progression (2–5 mm/min) in CSD, and the topography of the cortical spread, are comparable to the evolution of the BOLD signal complex we observed during the visual aura (Fig. 6). Second, CSDs tend to stop their progression at major sulci (27)—not unlike what was observed at the parieto-occipital sulcus in subject P.R. (Fig. 4). Third, light-evoked visual responses are suppressed during CSD in rabbit, and recover in 15–30 min (2, 3). Our light-induced MR signals also were suppressed during visual aura, and they recovered with a time course very similar to that in experimental CSD. Finally, in both CSD and migraine aura, the first affected areas were the first to recover.

Our findings build on the recent observations of Cao *et al.* (19) in the following ways. First, we identified specific BOLD events in the visual cortex that appeared to be directly linked to the aura percept, in both space (retinotopy) and time. Throughout the progression of each aura, we found a unique BOLD perturbation in the corresponding regions of retinotopic visual cortex. Like the progression of the aura in the visual field, the BOLD perturbations progressed from the representation of paracentral to more peripheral eccentricities—and these BOLD changes were found only in the hemisphere corresponding to the aura. Second, we were able to identify a source of the aura-related BOLD changes. Surprisingly, that source was in extrastriate visual cortex (area V3A) rather than in striate cortex (V1). Third, we were able to measure the rate of spread of the BOLD perturbations across the flattened cortical gray matter, and we

found it to be consistent with previous measures of CSD. Finally, it is worth noting that our migraine auras were not provoked by the visual stimuli. For example, interictal scans with identical visual stimuli did not produce auras nor migraines. Therefore our measurements were not confounded by the inducing stimulus. Evidence of spreading BOLD signal change during the light off periods also dissociated the BOLD perturbations from light stimulation.

Consistent with our findings, and as reported earlier in experimental animals (4), the spread of induced CSD was confined to the hemisphere in which it was initiated. James *et al.* (4) demonstrated in a gyrencephalic brain BOLD and apparent diffusion coefficient changes (ADC) due to CSD. They showed a clear temporal relation and an inverse correlation between these two measures, with an increase in BOLD signal paralleling a decrease in ADC. The magnitude of the BOLD signal change they measured (4–6% at 2 T) is comparable to that reported in our subjects.

We conclude that migraine aura is not evoked by ischemia (19, 52). More likely, it is evoked by aberrant firing of neurons and related cellular elements characteristic of CSD, and vascular changes develop due to fluctuations in neuronal activity during the visual aura. Drugs that inhibit the development and propagation of CSD provide novel treatment targets for both migraine aura, even before headache onset, as well as for stroke. Future studies using similar techniques should clarify the BOLD correlate of the onset of the headache pain, to better understand the relationship between CSD and pain.

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review-article

Pathophysiology of the migraine aura

The spreading depression theory

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The Characteristic form and development of sensory disturbances during migraine auras suggests that the underlying mechanism is a disturbance of the cerebral cortex, probably the cortical spreading depression (CSD) of Leão. The demonstration of unique changes of brain blood flow during attacks of migraine with aura, which have been replicated in animal experiments during CSD, constitutes another important line of support for the 'spreading depression' theory, which may be a key to an understanding of the migraine attack. Cortical spreading depression is a short-lasting depolarization wave that moves across the cortex at a rate of 3–5 mm/min. A brief phase of excitation heralds the reaction which is immediately followed by prolonged nerve cell depression synchronously with a dramatic failure of brain ion homeostasis, efflux of excitatory amino acids from nerve cells and enhanced energy metabolism. Recent experimental work has shown that CSD in the neocortex of a variety of species including man is dependent on activation of a single receptor, the *N*-methyl-*D*-aspartate receptor, one of the three subtypes of glutamate receptors. The combined experimental and clinical studies point to fruitful areas in which to look for migraine treatments of the future and provide a framework within which important aspects of the migraine attack can be modelled.

migraine; cerebral blood flow; spreading cortical depression; glutamate; nitric oxide

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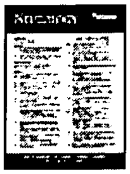

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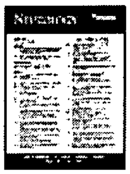

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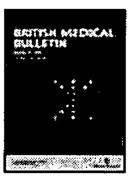

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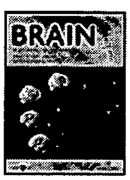

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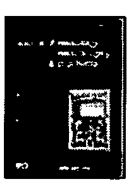

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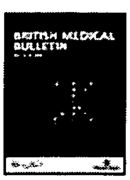

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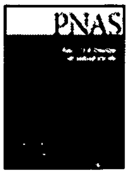

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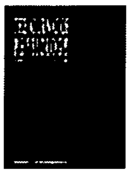

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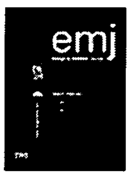

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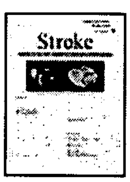

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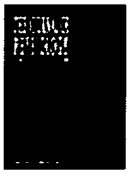

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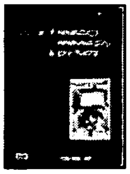

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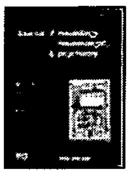

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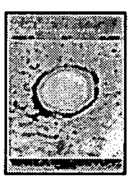

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